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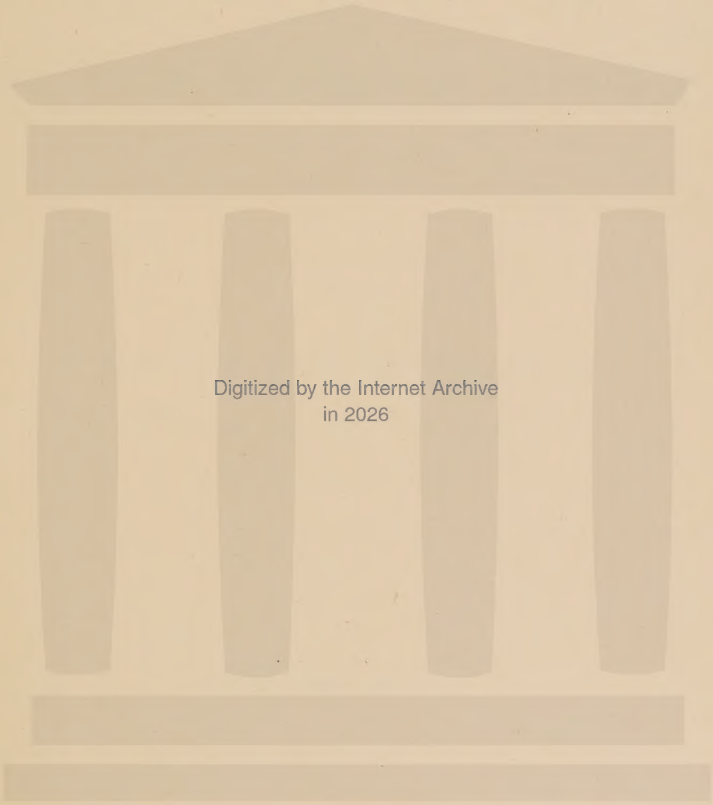
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OF THE

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TWENTY-NINTH SESSION

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MAY 12 AND 13, 1914

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1914

NOTICE

The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

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PHILADELPHIA

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W. S. THAYER, M.D.

ALTERNATE REPRESENTATIVE

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ASSOCIATION OF AMERICAN PHYSICIANS

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THEODORE C. JANEWAY, M.D.

ALTERNATE REPRESENTATIVE

RICHARD P. STRONG, M.D.

OFFICERS OF THE ASSOCIATION

FROM ITS ORGANIZATION TO THE PRESENT TIME

Year.	*President.*	*Vice-President.*	*Recorder.*	*Secretary.*	*Treasurer.*
1886.	Francis Delafield	.....	.....	James Tyson.	A. B. Ball.
1887.	S. Weir Mitchell.	Francis Minot. R. Palmer Howard.	J. T. Whittaker.	G. L. Peabody.	W. W. Johnston.
1888.	Wm. H. Draper.	Francis Minot. R. Palmer Howard	William Osler.	Henry Hun.	W. W. Johnston.
1889.	Francis Minot.	R. Palmer Howard. S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1900.	E. G. Janeway.	Wm. H. Welch.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1901.	Wm. H. Welch.	H. P. Walcott.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1902.	James C. Wilson.	Jas. Stewart.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1903.	James Stewart.	W. T. Councilman.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1904.	W. T. Councilman.	E. L. Trudeau.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1905.	E. L. Trudeau.	Frank Billings.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1906.	Frank Billings.	F. P. Kinnicutt.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1907.	F. P. Kinnicutt.	James Tyson.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1908.	James Tyson.	V. C. Vaughan.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1909.	V. C. Vaughan.	Henry Hun.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1910.	Henry Hun.	F. Forchheimer.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1911.	F. Forchheimer.	J. George Adami.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1912.	J. George Adami.	L. F. Barker.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1913.	L. F. Barker.	Simon Flexner.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1914.	Simon Flexner.	S. J. Meltzer.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1915.	S. J. Meltzer.	Henry Sewall.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.

ACTIVE MEMBERS

* Original Members

ELECTED

1892. Abbott, Alexander C., Laboratory of Hygiene, University of Pennsylvania, Philadelphia.
1896. Abel, John J., Station L., St. Charles Ave., Baltimore, Md.
1894. Adami, J. George, Pathological Laboratory, McGill University, Montreal, Canada.
1905. Adams, Samuel S., 1801 Connecticut Ave., Washington, D. C.
1896. Adler, Isaac, 22 East 62d St., New York.
1911. Anders, James M., 1605 Walnut St., Philadelphia.
1913. Anderson, John F., Public Health Service, Washington, D. C.
1911. Ashford, Bailey K., U. S. Army, San Juan, P. R.
1913. Auer, John, 13 West 121st St., New York.
1905. Babcock, Robert H., 77 East Washington St., Chicago.
1908. Baldwin, E. R., Saranac Lake, N. Y.
1899. Barker, L. F., 1035 North Calvert St., Baltimore, Maryland.
1894. Biggs, Herman M., 5 West 58th St., New York.
1895. Billings, Frank, 335 East 22d St., Chicago.
1898. Blackader, A. D., 236 Mountain St., Montreal, Canada.
1901. Blumer, George, 204 York St., New Haven, Conn.
1913. Boggs, Thomas R., 21 West Chase St., Baltimore, Md.
1892. Bolton, B. Meade, 54 Hammond Ct., Washington, D. C.
1890. Bond, Charles S., 112 North 10th St., Richmond, Ind.
1898. Brannan, John W., 11 West 12th St., New York.
1913. Brooks, Harlow, 44 West 9th St., New York.
1911. Brown, Lawrason, 104 Main St., Saranac Lake, N. Y.
1914. Brown, Thomas R., 19 W. Biddle St., Baltimore.
1904. Brown, Philip K., No. 2, 25th Ave., San Francisco, Cal.
1913. Bunting, C. H., University of Wisconsin, Madison.
1899. Cabot, R. C., 1 Marlborough St., Boston.
1912. Camac, C. N. B., 128 E. 60th St., New York.
1914. Cannon, Walter B., Harvard Med. School, Boston.
1908. Capps, Joseph A., 150 Michigan Ave., Chicago.
1889. Cary, Charles, 340 Delaware Ave., Buffalo, N. Y.
1907. Christian, Henry A., 252 Marlboro St., Boston.
1898. Cohen, Solomon Solis, 1525 Walnut St., Philadelphia.

ELECTED

1909. Cole, Rufus I., 65 East 77th St., New York.
1914. Coleman, Warren, 58 West 55th St., New York.
1904. Collins, Joseph, 37 West 54th St., New York.
1908. Conner, Lewis A., 121 East 62d St., New York.
1906. Coplin, W. M. L., 606 South 48th St., Philadelphia.
1888. Dana, Charles L., 53 West 53d St., New York.
1893. Dock, George, 600 S. Kingshighway, St. Louis, Missouri.
1904. Edsall, David L., 80 Marlborough St., Boston, Mass.
1901. Edwards, Arthur R., 100 State St., Chicago.
1888. Ernst, Harold C., 8 Greenough Ave., Jamaica Plain, Mass.
1900. Ewing, James, 260 West 57th St., New York.
1904. Finley, Frederick G., 1013 Dorchester St., Montreal, Canada.
1895. Fischel, W. E., 2647 Washington Ave., St. Louis..
1895. Flexner, Simon, Rockefeller Institute for Medical Research, 66th Street and Avenue A, New York.
1913. Ford, W. W., 1134 Cathedral St., Baltimore, Md.
1908. Freeman, R. G., 211 57th St., New York.
1913. Friedenwald, Julius, 1013 N. Charles St., Baltimore, Md.
1894. Fussell, M. Howard, 421 Lyceum Ave., Manayunk, Phila.
1903. Futcher, Thomas B., 23 West Franklin St., Baltimore.
1914. Gay, Frederick P., University of California, Berkeley.
1904. Gordinier, H. C., 89 4th St., Troy, N. Y.
1901. Greene, Charles L., 150 Lowry Arcade, St. Paul.
1890. Griffith, J. P. Crozer, 1810 Spruce St., Philadelphia.
1908. Hamilton, W. F., 287 Mountain St., Montreal, Canada.
1890. Hare, Hobart A., 1801 Spruce St., Philadelphia.
1898. Herrick, James B., People's Gas Building, Chicago.
1910. Hewlett, Albion W., 902 Baldwin Ave., Ann Arbor, Mich.
1900. Holt, L. E., 14 West 55th St., New York.
1911. Hoover, C. F., 702 Rose Building, Cleveland, Ohio.
1914. Howard, Campbell P., Iowa City, Iowa.
1911. Howard, W. T., Western Reserve Univ., Cleveland, Ohio.
1911. Howland, John, Johns Hopkins Hospital, Baltimore, Md.
*1886. Hun, Henry, 149 Washington Ave., Albany, N. Y.
1907. Hunt, Reid, Harvard Med. School, Boston.
1901. Jackson, Henry, 380 Marlborough St., Boston.
1908. Janeway, Theodore C., Johns Hopkins Hospital, Baltimore.
1902. Joslin, E. P., 81 Bay State Road, Boston.
1901. Kinyoun, J. J., 1421 Clifton St., Washington, D. C.
1902. Kober, Geo. M., 1819 Q St. N. W., Washington, D. C.
1900. Koplik, Henry, 30 East 62d St., New York.
1895. Lafleur, Henri A., 251 Peel St., Montreal, Canada.
1906. Lambert, Samuel W., 130 East 35th St., New York.

ELECTED

1913. Leathes, John B., University of Toronto, Toronto, Can.
1888. Lewis, Morris J., 1316 Locust St., Philadelphia.
1910. Libman, E., 180 East 64th St., New York.
1912. Locke, Edwin A., 311 Beacon St., Boston.
1911. Loeb, Leo, Barnard Skin and Cancer Hospital, St. Louis.
1909. Longcope, Warfield T., 680 Madison Avenue, New York.
*1886. Longstreth, Morris, 101 Brattle St., Cambridge, Mass.
1910. Lord Frederick T., 305 Beacon St., Boston.
1914. McCrae, John, 160 Metcalf Street, Montreal.
1905. McCrae, Thomas, 1627 Spruce St., Philadelphia.
1891. McPhedran, A., 151 Bloor St., Toronto, Canada.
1902. MacCallum, W. G., 437 W. 59th St., New York.
1905. Macallum, A. B., University of Toronto, Toronto, Canada.
1898. Mallory, F. B., Harvard Medical School, Boston.
1903. Martin, Charles F., 33 Durocher St., Montreal, Canada.
1892. Meltzer, S. J., 13 West 121st St., New York.
1905. Meyer, Adolph, Johns Hopkins Medical School, Baltimore.
1905. Miller, Joseph L., 122 S. Michigan Boulevard, Chicago.
1898. Mitchell, John K., 1730 Spruce St., Philadelphia.
1908. Moffitt, Herbert C., 240 Stockton St., San Francisco, Cal.
1914. Norris, Geo. W., 1530 Locust Street, Philadelphia.
1891. Northrup, W. P., 57 East 79th St., New York.
1900. Novy, F. G., University of Michigan, Ann Arbor, Michigan.
1902. Opie, E. L., 600 S. Kingshighway, St. Louis, Missouri.
1899. Park, Wm. H., 315 West 76th St., New York.
1904. Pearce, R. M., 2114 De Lancey Place, Philadelphia.
1909. Pratt, Joseph H., 317 Marlborough St., Boston.
1903. Preble, Robert B., 590 Dearborn Ave., Chicago.
1899. Prince, Morton, 458 Beacon St., Boston.
*1886. Putnam, James J., 106 Marlborough St., Boston.
1894. Rachford, B. K., 323 Broadway, Cincinnati.
1904. Richardson, Mark W., 145 State House, Boston.
1905. Riesman, David, 1715 Spruce St., Philadelphia.
1907. Rosenau, M. J., Harvard Medical School, Boston, Mass.
1911. Rudolf, Robert D., 396 Bloor St., Toronto, Canada.
1911. Russell, Frederick F., Surgeon-General's Office, U. S. Army, Washington, D. C.
1898. Sachs, B., 135 Central Park West, New York.
1908. Sailer, Joseph, 1830 Spruce St., Philadelphia.
1900. Sewall, Henry, 1360 Vine St., Denver, Col.
1902. Sippy, B. W., 122 S. Michigan Avenue, Chicago, Ill.
1892. Smith, Theobald B., South St., Forest Hills, Boston.
1907. Sollmann, Torald H., 4327 Superior Ave., Cleveland.

ELECTED

1898. Stengel, Alfred, 1728 Spruce St., Philadelphia.
1889. Stockton, Charles G., 436 Franklin St., Buffalo, N. Y.
1911. Strong, R. P., Harvard Medical School, Boston.
1907. Taylor, A. E. University of Pennsylvania, Philadelphia.
1899. Thacher, J. S., 20 West 50th St., New York.
1897. Thayer, W. S., 406 Cathedral St., Baltimore.
1889. Thompson, W. Gilman, 34 East 21st St., New York.
1889. Thomson, Wm. H., 23 East 47th St., New York.
1912. Tileston, Wilder, 308 Crown St., New Haven.
1889. Vaughan, Victor C., University of Michigan, Ann Arbor, Mich.
1898. Vickery, Herman F., 263 Beacon St., Boston.
1914. Wadsworth, Aug. B., 278 Yates St., Albany.
1901. Warthin, Alfred S., Univ. of Michigan, Ann Arbor, Mich.
1906. Weaver, George H., 1743 W. Harrison St., Chicago.
1898. Wesbrook, F. F., State Board of Health, Minneapolis, Minn.
1912. Wells, H. G., Sprague Memorial Institute, Chicago.
1913. Whipple, Geo. H., Hooper Foundation, University of California Hospital, San Francisco, California.
1914. Wilbur, Ray L., Sacramento and Webster Sts., San Francisco.
1894. Williams, Francis H., 505 Beacon St., Boston.
1901. Williams, Herbert U., University of Buffalo, Buffalo, N. Y.
1912. Wilson, Louis B., 1101 W. Zumbro St., Rochester, Minn.
1898. Withington, Charles F., 35 Bay State Road, Boston.
1914. Wood, Francis C., 437 W. 59th St., New York.

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1914. Bass, Charles C., Tulane Univ., New Orleans.
1914. Brill, Nathan E., 48 W. 76th St., New York.
1913. Duval, Charles, W., Tulane University, New Orleans.
1913. Hamman, Louis V., 714 Park Ave., Baltimore, Md.
1911. Klotz, Oskar, University of Pittsburgh, Pittsburgh, Pa.
1913. Landis, H. R. M., 11 South 21st St., Philadelphia.
1913. Morris, Roger S., Clifton Springs, N. Y.
1914. Ordway, Thomas, Harvard Med. School, Boston.
1914. Peabody, Francis W., Brigham Hospital, Boston.
1914. Pemberton, Ralph, 2224 Locust St., Philadelphia.
1914. Plummer, H. S., Rochester, Minn.
1913. Robinson, G. Canby, 600 S. Kingshighway, St. Louis.
1914. Rous, Peyton, 123 E. 62 St., New York.
1913. Rowntree, Leonard G., Johns Hopkins Univ., Baltimore.
1914. Smith, Elsworth, Humboldt Building, St. Louis.
1913. Southard, Elmer S., Harvard Med. School, Boston.
1911. Taussig, Albert E., Metropolitan Building, St. Louis.
1913. White, Franklin W., 322 Marlborough St., Boston.
1913. White, Wm. Charles, Univ. of Pittsburgh, Pittsburgh, Pa.
1914. Wood, Edward Jenner, 201 Chestnut St., Wilmington, N. C.
1914. Woodyatt, Rollin Turner, 104 S. Mich. Ave., Chicago.

HONORARY MEMBERS

* Original Members

Elected Active Member	Elected Honorary Member	
*1886.	1912.	Jacobi, A., 19 East 47th St., New York.
*1886.	1912.	Osler, Wm., Oxford University, England.
*1886.	1913.	Prudden, T. Mitchell, 160 W. 59th St., New York.
*1886.	1913.	Welch, William H., 807 St. Paul St., Baltimore, Md.

EMERITUS MEMBERS

* Original Members

Elected Active Member	Elected Emeritus Member	
1888.	1910.	Bridge, Norman, 10 Chester Place, Los Angeles, Cal.
*1886.	1897.	Chew, Samuel C., 215 West Lanvale St., Baltimore.
*1886.	1906.	Councilman, Wm. T., 78 Bay State Road, Boston.
1894.	1908.	Cutler, Elbridge G., 214 Beacon St., Boston.
1897.	1905.	Cushny, Arthur C., University of London, London, England.
*1886.	1907.	Delafield, Francis A., 5 West 50th St., New York.
*1886.	1905.	Edes, Robert T., 340 Summer Ave., Reading, Mass.
1890.	1902.	Fisk, S. A., Brimfield, Mass.
*1886.	1900.	Guitéras, John, Havana, Cuba.
*1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1897.	1910.	Hektoen, Ludvig, Rush Medical College, Chicago.
*1886.	1908.	Henry, Frederick P., 114 S. 18th St., Philadelphia.
1890.	1902.	Hurd, H. M., Johns Hopkins Hospital, Baltimore.
1899.	1914.	James, Walter B., 17 W. 54th St., New York.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
1901.	1913.	Morse, John L., 70 Bay Street Road, Boston.
*1886.	1911.	Peabody, Geo. L., Newport, R. I.
1898.	1914.	Pfaff, Franz, Dresdner Bank, Berlin.
*1886.	1898.	Polk, Wm. M., 7 East 36th St., New York.
*1886.	1904.	Robinson, Beverley, 42 West 37th St., New York.
1900.	1914.	Sears, Geo. G., 19 Marlborough St., Boston, Mass.
*1886.	1912.	Shattuck, Frederick C., 135 Marlborough Street, Boston.
*1886.	1905.	Shattuck, George B., 183 Beacon St., Boston.
*1886.	1914.	Smith, A. A. 18 W. 51st Street, New York.
1887.	1902.	Starr, Louis, 1818 S. Rittenhouse Square, Phila.
1887.	1911.	Starr, M. Allen, 5 West 54th St., New York.

Elected Active Member	Elected Emeritus Member	
*1886.	1907.	Sternberg, George M., 2005 Massachusetts Ave., N. W., Washington, D. C.
*1886.	1906.	Trudeau, Edward L., Saranac Lake, N. Y.
*1886.	1912.	Tyson, James, 1506 Spruce St., Philadelphia.
1889.	1904.	Walcott, Henry P., 11 Waterhouse St., Cambridge, Mass.
*1886.	1912.	Ward, Samuel B., 281 State St., Albany.
*1886.	1911.	Wilkins, George, 899 Dorchester St., Montreal.
*1886.	1911.	Wilson, James C., 1509 Walnut St., Philadelphia.
*1886.	1908.	Wood, Horatio C., 4107 Chester Ave., Philadelphia.
1899.	1912.	Wright, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston

DECEASED MEMBERS

* Original Members

Date of Election

*1886. Atkinson, I. E., Baltimore.
*1886. Ball, A. Brayton, New York.
1890. Barker, Fordyce, New York.
*1886. Baumgarten, G., St. Louis.
*1886. Billings, John S., New York.
*1886. Bowditch, Henry I., Boston.
*1886. Bruen, Edward T., Philadelphia.
*1886. Busey, Samuel C., Washington, D. C.
1907. Carroll, James, Washington, D. C.
*1886. Clark, Alonzo, New York.
*1886. Clymer, Meredith, New York.
*1886. Da Costa, J. M., Philadelphia.
1889. Dabney, William C., University of Virginia.
*1886. Dalton, John C., New York.
*1886. Dana, Israel T., Portland, Maine.
1888. Danforth, I. N., Chicago.
*1886. Donaldson, Frank, Baltimore.
*1886. Draper, William H., New York.
1899. Ely, John Slade, New Haven, Conn.
*1886. Fitz, Reginald H., Boston.
*1886. Folsom, Chas. F., Boston.
*1886. Forchheimer, F., Cincinnati.
*1886. Formad, Henry F., Philadelphia.
1889. Geddings, W. H., Atken, S. C.
*1886. Graham, J. E., Toronto, Canada.
1898. Herter, C. A., New York.
*1886. Howard, R. Palmer, Montreal, Canada.
*1886. Hudson, E. Darwin, Jr., New York.
*1886. Hutchinson, James H., Philadelphia.
*1886. Janeway, E. G., New York.
*1886. Johnson, Hosmer A., Chicago.
1899. Johnston, W. G., Montreal, Canada.
*1886. Johnston, W. W., Washington, D. C.
1902. Kelly, A. O. J., Philadelphia.

Date of Election

*1886. Kinnicutt, Francis P., New York.
1890. Latimer, Thomas S., Baltimore.
*1886. Leidy, Joseph, Philadelphia.
*1886. Loomis, Alfred L., New York.
1889. Loving, Starling, Columbus, O.
*1886. Lyman, Henry M., Chicago.
1890. MacDonnell, R. P., Montreal, Canada.
*1886. McBride, Thomas A., New York.
1887. Meigs, Arthur V., Philadelphia.
*1886. Metcalfe, John T., Cold Spring, N. Y.
*1886. Miles, F. T., Baltimore.
*1886. Minot, Francis, Boston.
*1886. Mitchell, S. Weir, Philadelphia.
1887. Musser, John H., Philadelphia.
1898. Packard, Frederick A., Philadelphia.
*1886. Pepper, William, Philadelphia.
1888. Prentiss, D. W., Washington, D. C.
1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo, N. Y.
1889. Roosevelt, J. West, New York.
*1886. Ross, George, Montreal, Canada.
1893. Rotch, Thomas M., Boston.
*1886. Schmidt, H. D., New Orleans.
*1886. Sinkler, Wharton, Philadelphia.
1891. Smith, Andrew H., New York.
1905. Steele, J. Dutton, Philadelphia.
1896. Stewart, D. D., Philadelphia.
*1886. Stewart, James, Montreal, Canada.
*1886. Stillé, Alfred, Philadelphia.
*1886. Thacher, James K., New Haven, Conn.
*1886. Whittaker, James T., Cincinnati.

ASSOCIATION

OF

AMERICAN PHYSICIANS

CONSTITUTION

As Amended May 15, 1912

ARTICLE I

OBJECT AND NAME

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

ARTICLE II

MEMBERS

The number of active members shall be limited to one hundred and sixty. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to emeritus membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of honorary members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

ARTICLE III

OFFICERS

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

ARTICLE IV

DUTY OF OFFICERS

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of TRANSACTIONS.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

ARTICLE V

COUNCIL

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate,

and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

ARTICLE VI

MEETINGS

1. The Association shall hold an annual meeting either in the City of Washington, D. C., or at Atlantic City at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. The President shall have complete charge of, and responsibility for, the program. He shall have power to accept or reject any paper offered. He shall have power to limit the number of papers, and to assign a time limit for each one. Papers shall be presented to the Association only in abstract, and preferably shall not be read from manuscript. They may be published in full in the TRANSACTIONS as also in any other medical publication.

5. The referee, co-referee, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

ARTICLE VII

QUORUM

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum, and for altering the Constitution twenty-five members shall be necessary.

ARTICLE VIII

ELECTION OF MEMBERS

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting

of the Association; and within six months of the time of nomination the nominators shall transmit to the Council letters stating the qualifications of the nominee and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The elections of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

ARTICLE IX

ANNUAL DUES

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

ARTICLE X

AMENDMENTS TO THE CONSTITUTION

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

TWENTY-NINTH ANNUAL MEETING

Held at Atlantic City, New Jersey, May 12 *and* 13, 1914

The following members were present at the meeting:

A. C. Abbott,
I. Adler,
J. M. Anders,
J. Auer,
L. F. Barker,
H. M. Biggs,
G. Blumer,
T. R. Boggs,
H. Brooks,
T. R. Brown,
R. C. Cabot,
J. A. Capps,
H. A. Christian,
S. S. Cohen,
R. I. Cole,
W. Coleman,
W. M. L. Coplin,
G. Dock,
D. L. Edsall,
F. G. Finley,
S. Flexner,
W. W. Ford,
R. G. Freeman,
J. Friedenwald,
M. H. Fussell,
T. B. Futcher,
J. P. C. Griffith,
L. V. Hamman,
W. F. Hamilton,
H. A. Hare,
J. B. Herrick,
A. W. Hewlett,
C. P. Howard,
A. Jacobi,
E. P. Joslin,
G. M. Kober,
H. Koplik,
H. R. M. Landis,
E. Libman,
E. A. Locke,
W. T. Longcope,
M. Longstreth,
John McCrae,
T. McCrae,
A. McPhedran,
W. G. MacCallum,
A. B. Macallum,
S. J. Meltzer,
J. L. Miller,
H. C. Moffitt,
R. S. Morris,
G. W. Norris,
E. L. Opie,
R. M. Pearce,
J. H. Pratt,
D. Riesman,
L. G. Rowntree,
F. F. Russell,
B. Sachs,
J. Sailer,
H. Sewall,
F. C. Shattuck,
E. S. Southard,
A. Stengel,
R. P. Strong,
A. E. Taussig,
A. E. Taylor,
J. S. Thacher,
W. S. Thayer,

W. G. Thompson,
W. H. Thomson,
W. Tileston,
J. Tyson,
A. B. Wadsworth,
A. S. Warthin,
Wm. H. Welch,
G. H. Whipple,
F. W. White,
W. C. White,
F. H. Williams,
L. B. Wilson,
C. F. Withington,
F. C. Wood.

Tuesday, May 12

Morning Session.—The Association met in the solarium of the Marlborough-Blenheim Hotel, and was called to order at 10 A.M., by the President, Dr. Simon Flexner, of New York, who delivered the President's address.

The Secretary presented the following recommendations from the Council:

That the annual dues for the ensuing year be as follows: Salaried laboratory workers, $5.00; associate members, $7.50, and practitioners, $15.00, and that the Transactions of the Association be furnished upon application to Emeritus Members at $4.00 per volume.

The Council also recommends that the Recorder be authorized to dispose of old sets of the Transactions at the rate of $2.50 per volume for paper bound copies, and $3.00 for the cloth bound copies.

On account of unusual delay in issuing the volume of Transactions of last year, the Council recommends that the time limit for papers to receive consideration for publication be not later than October 16. Upon motion these recommendations were adopted.

The Secretary reported that the Council recommends to the Association for election the following officers for the ensuing year:

President, Dr. S. J. Meltzer, New York; *Vice-President*, Dr. Henry Sewall, Denver, Colo.; *Secretary*, Dr. Geo. M. Kober, Washington, D. C.; *Recorder*, Dr. Thomas McCrae, Philadelphia, Pa.; *Treasurer*, Dr. J. P. Crozer Griffith, Philadelphia, Pa.; *Councillor*, Dr. W. S. Thayer, Baltimore, Md.; *Representative on the Executive Committee of the Congress of American Physicians and Surgeons*, Dr. Theodore C. Janeway, New York; *Alternate Representative*, Dr. Richard P. Strong, Boston, Mass.

The Council also reports favorably upon the following nominees for active and associate members:

Active Members: Thomas R. Brown, Baltimore; Walter B. Cannon, Boston; Warren Coleman, New York; Frederick P. Gay, Berkeley; Campbell P. Howard, Iowa City; John McCrae, Montreal; George W. Norris, Philadelphia; Augustus B. Wadsworth, New York; Ray L. Wilbur, San Francisco; Francis Carter Wood, New York.

The following were recommended as associate members:

Associate Members: Charles C. Bass, New Orleans; Nathan E. Brill, New York; Thomas Ordway, Boston; Francis W. Peabody, Boston; Ralph Pemberton, Philadelphia; H. S. Plummer, Rochester, Minn.; Peyton Rous, New York; Elsworth Smith, St. Louis; Edward Jenner Wood, Wilmington, N. C.; Rollin Turner Woodyatt, Chicago, Ill.

The Treasurer presented his report, which was referred to an auditing committee consisting of Drs. Sailer and Opie, with instructions to report as early as possible.

Dr. James Tyson, Chairman of a special committee appointed for the purpose of coöperating with the George Washington Memorial Association in securing funds for the erection of a permanent home for scientific societies in the City of Washington, reported that a circular was sent out last year which resulted in the collection of $190.00, which was paid to the Treasurer, with some promises of further contributions or subscriptions. The committee has been unfortunate in losing two of its members by death, Drs. Mitchell and Fitz, and by appointment Dr. Frederick C. Shattuck filled the vacancy caused by the death of Dr. Mitchell. The other vacancy has not yet been filled, this appointment being left to the President.

The President stated that this seemed to be a favorable opportunity for promoting such an object as this. The Government has offered the George Washington Memorial Association a site for this memorial hall, provided the sum of one million dollars can be subscribed by the various parties interested, and until such sum has been subscribed the Government's offer is not available. Five thousand dollars should be raised by this Association, if it is pos-

sible to do so. He expressed the hope that Dr. Tyson would act as Chairman, and Dr. Shattuck as associate.

The reading of papers was then proceeded with.

Dr. Joseph Sailer read a paper entitled "Chronic Interstitial Gastritis," which was discussed by Dr. David Riesman.

Dr. S. J. Meltzer followed with a contribution on "The Nature of Peristalsis and the Action of Magnesium Sulphate."

This paper was discussed by Dr. Barker, and the discussion closed by Dr. Meltzer.

Dr. Julius Friedenwald read a paper entitled "Clinical Study of a Thousand Cases of Cancer of the Stomach." (No discussion.)

Dr. Solomon Solis Cohen read a paper entitled "When and How to Use Tuberculin in Private Practice."

The paper was discussed by Dr. Jacobi.

Dr. Henry Sewall read a paper entitled "Some Relations of the Brain and of the Olfactory Apparatus to the Processes of Immunity." (No discussion.)

Dr. Warren Coleman and Dr. John A. Hartwell contributed a joint paper entitled "Report of a Case of Splenectomy for Pernicious Anemia."

Dr. Herbert C. Moffitt followed with a paper entitled "Studies in Pernicious Anemia."

These two papers were discussed together by Drs. Thayer, Miller, Libman, and Pearce.

Dr. I. Adler presented a paper entitled "Studies in Experimental Arteriosclerosis." (No discussion.)

Dr. R. C. Cabot, Boston, read a paper entitled "Mitral Stenosis; Observations on Two Hundred Cases Before and After Death."

This paper was discussed by Drs. Herrick, Sewall, Thayer, and Barker, and in closing by Dr. Cabot.

Dr. Alexander McPhedran, Toronto, read a paper on "Recurrent Fever in a Case of Aortic Aneurysm." (No discussion.)

Dr. Joseph Sailer reported that the auditing committee had examined the accounts of the Treasurer and had found them correct.

Adjourned at 1 P.M.

Afternoon Session.—The Association reassembled at 2 P.M., and was called to order by the President.

Drs. W. F. Hamilton and Maude E. Abbott presented a joint paper entitled "A Case of Patent Ductus Arteriosus, with Infective Pulmonary Endarteritis," which was discussed by Drs. Thayer, Jacobi, Tileston, and Libman.

Dr. W. S. Thayer read a paper entitled "Certain Tests of Renal Function," which was discussed by Drs. Withington, Miller, and in closing by Dr. Thayer.

Dr. A. E. Taylor and Dr. R. M. Pearce presented a joint paper entitled "Osmotic Pressure in the Kidney of Nephritis," which was discussed by Dr. Macallum, and in closing by Dr. Taylor.

Dr. Alfred Stengel and Dr. J. Harold Austin read a joint paper entitled "Syphilitic Nephritis," which was discussed by Drs. Tyson, Shattuck, and Cohen.

Dr. Frederick C. Shattuck read a paper entitled "A Possible Factor in the Production and Distribution of Œdema." No discussion.)

Drs. Franklin W. White and Ralph D. Leonard read a joint paper entitled "*X*-ray Evidence in Early and Latent Cancer of the Stomach." (No discussion.)

Drs. Louis B. Wilson and I. W. McDowell presented a joint paper entitled "Further Report on the Pathologic Evidence of the Relationship between Ulcer and Gastric Cancer." (No discussion.)

Dr. Albert E. Taussig read a paper entitled "The Inspiratory Exaggeration of the Dicrotic Wave in Pericarditis," which was discussed by Dr. Sewall.

Dr. F. C. Wood read a paper entitled "The Action of Radium on Tumors in Mice." (No discussion.)

Dr. L. F. Barker read a paper entitled "Abnormalities of Secretion of the Sex Glands." (No discussion.)

Dr. George Dock read a paper entitled "So-called Intra-uterine Amputation," which was discussed by Dr. Jacobi, Dr. Dock closing the discussion.

Dr. Richard P. Strong read a paper entitled "The Etiology of Some of the Tropical Granulomata," which was discussed by Dr. Flexner, Dr. Strong closing the discussion.

Adjourned at 4.45 P.M.

Wednesday, May 13

Morning Session.—The Association met at 10 A.M., and was called to order by the President. The first order of business was the election of officers and members. Drs. Miller and Futcher were appointed as tellers.

The result of the ballot was that the following officers, members and associate members, were duly elected:

President—S. J. Meltzer.

Vice-President—Henry Sewall.

Secretary—George M. Kober.

Recorder—Thomas McCrae.

Treasurer—J. P. Crozer Griffith.

Councillor—W. S. Thayer.

Representative on the Executive Committee of the Congress of American Physicians and Surgeons—Theodore C. Janeway.

Alternate Representative—Richard P. Strong.

Active Members—Thomas R. Brown, Baltimore; Walter B. Cannon, Boston; Warren Coleman, New York; Frederick P. Gay, Berkeley; Campbell P. Howard, Iowa City; John McCrae, Montreal; George W. Norris, Philadelphia; Augustus B. Wadsworth, New York; Ray L. Wilbur, San Francisco; Francis Carter Wood, New York.

Associate Members—Charles C. Bass, New Orleans; Nathan E. Brill, New York; Thomas Ordway, Boston; Francis W. Peabody, Boston; Ralph Pemberton, Philadelphia; H. S. Plummer, Rochester, Minn.; Peyton Rous, New York; Elsworth Smith, St. Louis; Edward Jenner Wood, Wilmington, N. C.; Rollin Turner Woodyatt, Chicago.

Dr. Thomas R. Brown read a paper entitled "The Normal Amount of Diastatic Ferment in the Urine and Feces and its Variation in Diseases of the Pancreas."

Dr. Geo. H. Whipple read a paper entitled "Liver Function as Influenced by the Ductless Glands in Experimental Conditions."

Dr. L. G. Rowntree, Dr. E. K. Marshall, Jr., and Allan Chesney, read a joint paper entitled "Studies on Liver Function." These three papers were discussed together by Drs. Taylor, Howard, Tileston, Barker, Stengel, and in closing by Dr. Brown.

Dr. James M. Anders read a paper entitled "The Relation of Pituitary Disease to Glycosuria, with Statistics and the Report of an Interesting Case," which was discussed by Drs. Futcher and Warthin.

Dr. David L. Edsall and Dr. H. J. Means read a joint paper entitled "Observations on Respiration and Respiratory Metabolism," which was discussed by Dr. Meltzer.

Dr. John Auer presented a paper entitled "The Action of Sera With and Without Preservatives upon the Medullary Centres after Intraspinal Injections," which was discussed by Drs. Meltzer and Capps.

Dr. Joseph L. Miller read a paper entitled "Do Expectorants in Ordinary Therapeutic Doses Modify the Bronchial Secretions?" The paper was discussed by Drs. Meltzer, Sewall, Barker, Jacobi, and in closing by Dr. Miller.

Dr. William Hanna Thomson read a paper on "Aconite as a Vaso-dilator," which was discussed by Drs. Tyson, Jacobi, and the discussion was closed by Dr. Thomson.

Drs. Wilder Tileston and C. W. Comfort, Jr., read a joint paper entitled "The Non-protein Nitrogen and the Urea of the Blood in Health and in Disease, as Estimated by Folin's Method," which was discussed by Dr. W. H. Thomson.

Dr. John McCrae read a paper entitled "The Subcutaneous Administration of Oxygen as a Therapeutic Measure," which was discussed by Dr. Meltzer.

Drs. W. G. MacCallum and R. A. Lambert read a joint contribution on "The Effects of the Removal of Calcium From the Blood by Dialysis," which was discussed by Dr. Meltzer.

Dr. B. Sachs read a paper on "Infectious and Toxic Forms of Transverse Myelitis," which was discussed by Dr. Flexner, and the discussion closed by Dr. Sachs.

Adjourned at 1.15 P.M.

Afternoon Session.—The Association was called to order at 2.30 P.M.

Dr. E. E. Southard read a paper on "Microscopic Evidence as to the Organic Nature of Dementia Præcox," which was discussed by Dr. Cabot and in closing by Dr. Southard.

Dr. A. S. Warthin read a paper on "The Persistence of Spirocheta Pallida in Tissues of Clinically Cured Cases of Syphilis (after Thorough Treatment, Absence of Symptoms and Repeated Negative Wassermanns)," which was discussed by Dr. Welch, and the discussion closed by Dr. Warthin.

Drs. E. L. Opie and L. B. Alfort read a joint paper on "The Effect of Diet Upon the Toxicity of Substances which Produce Hepatic Lesions or Nephritis," which was discussed by Dr. Meltzer.

Dr. Joseph A. Capps and Dr. B. J. Davis presented a paper on "An Epidemic of Streptococcus Sore Throat in Jacksonville, Ill., which was Traced to the Milk of Cows Affected with Streptococcus Mastitis." This paper was discussed by Drs. Kober, Cabot, and the discussion closed by Dr. Capps.

Dr. William Charles White read a paper on "The Influence of Benzol Inhalations on Experimental Pulmonary Tuberculosis in Rabbits." (No discussion.)

Dr. Philip King Brown, and Dr. W. Taylor Cummins presented a paper on "A Differential Study of Coccidioidal Disease and Blastomycosis from a Pathological and Bacteriological Standpoint," which was discussed by Dr. Welch, and the discussion closed by Dr. Cummins.

Dr. Harlow Brooks read a paper entitled "Heredity in Bovine Tuberculosis." (No discussion.)

The following papers were read by title: "Botulism; Report of a Group of Cases with One Autopsy," by Drs. R. L. Wilbur and Wm. Ophüls; "The Effect of Intraspinal Injections of Serum Containing Certain Antiseptics," by Drs. John F. Anderson and Carl Voegtlin; "Pathogenesis of Poliomyelitis in the Light of Recent Experiments," by Dr. Simon Flexner.

On motion of Dr. Thayer, which was duly seconded and carried, a vote of thanks was extended to the retiring President, Dr. Flexner, for the preparation of a program of unusual interest and importance, and for the able and impartial manner in which he had presided over the deliberations of the Association.

Adjourned at 4.30 P. M.

GEORGE M. KOBER,
Secretary.

THE ADDRESS OF THE PRESIDENT

THE FULL-TIME TEACHER OF MEDICINE

By SIMON FLEXNER, M.D.
NEW YORK

The Association has lost through death in the course of the last year four of its members: Dr. F. Forchheimer, Dr. Reginald H. Fitz, Dr. S. Weir Mitchell, and Dr. Thomas M. Rotch. Of these, three—Drs. Mitchell, Fitz and Forchheimer—were original members and past Presidents of the Association, and each of the four men represented an important phase of medical teaching and practice, and all played honorable and distinguished parts in their generation. Dr. Forchheimer was a prominent figure of modern type in the Ohio Valley; Dr. Rotch one of the few men who served to differentiate pediatrics from medicine; Dr. Fitz has the distinction of having offered at the Harvard Medical School, as far back as 1870, one of the first, perhaps the very first, regular courses in pathological anatomy ever given in this country; while of Dr. Mitchell's varied and brilliant achievements it is impossible to speak briefly. It is well, however, to recall that to a degree not generally appreciated he was the actual pioneer in this country in the application of physiological concepts and methods to clinical medicine. The world is the poorer and this Association the less distinguished in consequence of the loss of this notable group of men.

The privileges extended to your President graciously include freedom of selection from among the many eligible subjects the topic that seems to him most novel and significant at the moment. Availing myself of this opportunity I have chosen to confine my

brief remarks to the subject of the full-time teacher of medicine, as the latest evolutionary product of the modernization of medical education.

It is now twenty-eight years since the Association was founded—a period that has witnessed a revolution in the teaching and practice of medicine. The causes operating to produce the great change have been twofold: extension of the boundaries of knowledge, and the conversion of medical schools into departments of universities.

The rapid extension of knowledge coincided with and was in great measure the product of the active pursuit of physiology and pathology, bacteriology and pharmacology, either alone or in association with clinical studies, for which special laboratories and institutes came to be established. As was to be expected the advances in question were first made in Europe, where university organization was already favorable, to be followed in America when opportunity became propitious.

Development was very rapid indeed. A comparison of the state of university medical education, as it existed in America in 1886, with that now existing, cannot fail to cause a wholesome feeling of pride in all those who participated, as did many of the members of this Association in that fundamental work of regeneration. Where this forward movement has lagged behind, local conditions, in their nature temporary, have been and still are the causes; for our rapid progress leaves no room for doubt that a comprehensive scheme of university medical education embracing the entire country is both desirable and feasible.

The growth in medical knowledge and improvement in medical instruction are traceable in last analysis to the segregation of groups of men of scientific attainment and temper, who were thus enabled to work in a favorable environment; their sheltered situation protects them from the diversions and distractions of ordinary professional life, and encourages them to devote all available energies to the advancement of science and the teaching of students. In its strict form, segregation of this type has been limited to workers in laboratories, but in some degree it has related also to clinical teachers in hospitals.

Established midway in the course of the development that I have sketched, the independent institution for medical research has within a decade begun to exercise a distinct influence on medical progress. The foundation of these institutes was impossible until improved medical schools furnished an adequate supply of students whose training approximated that of the older European countries.

In turn, all these conditions have reacted more and more powerfully on clinical teaching. The professor of medicine in the university medical school ceased long ago to be the general practitioner. This could not have been otherwise; for not only has a steadily increasing demand for specialized knowledge, often of a highly technical character, been made of the clinical teacher, but the amount of knowledge to be communicated and the difficulty of the technique to be acquired, necessitate that more and more hours be spent in teaching in or adjacent to the hospital wards. It has thus become physically impossible for the teacher to remain in general practice and at the same time attend to his university duties. As a compromise he has undertaken to put his technical knowledge and experience at the service of the general practitioner who may refer to him his puzzling and desperate cases.

If you will reflect upon the meaning of this particular development, you will observe, I think, that a new type of clinical teacher distantly removed from the practitioner out of which class the earlier clinical teacher arose, has thus been evolved. He bears the stamp of the hospital; he is indeed fabricated within its walls. In notable instances in this country a residence of six or eight years within the hospital has constituted practically the entire clinical training that has sufficed to prepare both for the office of consultant and that of professor. The men I have in mind have never been family physicians, as that phrase is commonly used; they have derived the bulk of their experience from the dispensary and wards, and from the supplement of unusual and problematical or important cases which have sought them out from all parts of the country.

Nor can this state of things be regarded as merely accidental, since it was necessitated by the conditions surrounding the new medicine, although perhaps not obviously and at first sight. But

looking backward its inevitability is apparent. Clinical teaching enters today upon a new phase, becoming thereby more academic in character than ever before. But what is happening represents no sudden change, no complete transformation. The function of the clinical teacher has been newly defined within the past one or two decades, and a process of selection within the terms of this definition has been going forward. Hence we are confronted not so much by an experiment as by a development. The full-time clinical teacher is simply the consultant as developed in recent years, completely protected by his university status.

If my interpretation is correct the full-time or university clinical professorship will be encountered in other countries—in Great Britain and in Germany for example. Meanwhile it need not be surprising that, with institutions still as plastic as ours, so logical a development should have been first perceived and put into practical operation in America.

The Association of American Physicians has sympathized with every forward movement affecting the fortunes of medicine in this country. It therefore will observe this latest step, revolutionary though it may seem to many, with a single hope: that if it be in the real interest of medical progress, it may be given every chance to succeed.

WHEN AND HOW TO USE TUBERCULIN PREPARATIONS IN PRIVATE PRACTICE

EFFICACY OF ADMINISTRATION BY MOUTH

By SOLOMON SOLIS COHEN, M.D.
PHILADELPHIA

If tuberculin is to become a useful therapeutic agent, its administration must be made so safe and so simple that it can be employed without fear by the general practitioner. After all, it is but a very small proportion of the tuberculous who come under sanatorium care, or who seek the advice of "tuberculosis specialists;" and any treatment that must needs be restricted closely in its application can do but a minimum of good.

Thanks principally to Arthur Latham and his co-workers (H. D. Spitta and A. E. Inman), we have now a method of administration of tuberculin and similar bacterial products which meets the necessities of the situation.

The writer of this paper is among those who condemned and opposed the use of the so-called "Koch's lymph" when it was first—and, through the meddling of the German Emperor, prematurely—introduced. Both theory and observation were convincing as to its harmfulness in the overwhelming number of cases; and nothing of what was then said[1] needs be retracted.

But later work, and especially the painstaking studies of Trudeau, have shown not only the cause of the unfortunate results of the first period, but also how they may be avoided.

The early disasters were chiefly owing to two errors: (*a*) *crude*

[1] S. Solis Cohen, Therapeutics of Tuberculosis, in Hare's System of Practical Therapeutics, first edition, Philadelphia, 1891, vol. i, pp. 872 to 874.

dosage; and (*b*) *unsuitability of cases* treated. With due attention to the selection of cases, and with careful choice and gradation of doses, results are now reached that are well worth while, and that apparently cannot as yet be attained by other means.

It is especially incumbent, therefore, on those of us who combatted the destructive use of tuberculin, to do our part toward the establishment of its constructive use. This paper is so intended. It deals with *pulmonary tuberculosis* only. It will attempt to show *how* and *when* in general private practice, some of the preparations of tubercle bacilli and their derivatives may be employed as adjuvants to hygienic regime and wise medication, with distinct benefit to the patient. For sanatorium physicians it might be considered a work of supererogation; but it is addressed to the general practitioner, who can (and should be encouraged to) make use of this additional means of aiding recovery in a frequent and troublesome malady.

Dosage. Although it is necessary—for our purpose, at least—to modify his actual plan of operation, Trudeau[1] established the correct principle of dosage—namely, to begin with a minute dose and to induce tolerance (or immunity) by very gradual increase, with due regard to local, focal and constitutional reactions—including among the latter, such symptoms as headache and malaise, even in the absence of febrile movement. Trudeau followed the common custom of hypodermic injection, and was guided by clinical phenomena in estimating the effect of the remedy.

When Sir Almroth Wright introduced the study of the opsonic index, a further advance was made. Not only did a definite reaction subject to precise means of investigation become the criterion of effect, but also the differentiation between the positive and negative phases of the reaction did away with one source of danger and made possible the choice of the most favorable time for injection. The method, however, was, and is, too troublesome for general application and has not found favor, even among sanatorium physicians. It is of advantage in special instances, and particularly in the investigation of novel procedures, as a measure of control;

[1] Amer. Jour. Med. Sci., August, 1906, and June, 1907.

and by it, indeed, the studies of Latham and his colleagues were made demonstrative.

The next great advance came when Latham,[1] studying his cases clinically while Drs. Spitta and Inman verified the results by laboratory methods, demonstrated (1) that the clinical temperature curve furnished an exact and trustworthy method of distinguishing between the positive and negative phases of the tuberculo-opsonic reaction (the negative phase being denoted by a rise of temperature, the positive phase by a decline), and (2) that the administration of tuberculin products (and other bacterins) by the mouth (or rectum) was followed by reactions as definite and effective as those resulting from hypodermic injection. These results, the work of competent observers, and of methods of study beyond criticism, have made feasible the general, intelligent use of tuberculin; *i. e.*, its application outside of sanatoriums, hospitals, and the care of specialists with laboratory facilities and training.

Latham was able to show also that therapeutic reactions can be produced by doses of tuberculin even smaller than those employed by Trudeau.

Taking up Latham's methods, I observed[2] (*a*) that by certain modifications of the technic the administration of tuberculin *per os* might be made somewhat simpler, and thus more widely available; and (*b*) that the initial dose might with advantage be still further and very greatly reduced.

I then requested my nephew, Dr. Myer Solis-Cohen,[3] to make a further and independent series of observations, using various forms of tuberculin preparations. This study was confirmatory of both Latham's and my own results, and developed a new, and somewhat surprising feature, in the regularity with which in certain subjects definite constitutional reactions (chiefly headache and malaise) followed the administration *per os* of almost infinitesimal doses (*e. g.*, one one-billionth of a milligram) of *tuberculinum*

[1] Latham, Spitta and Inman, Proc. Royal Society of Medicine, London, 1907–1908, Medical Section, pp. 213 seq.; Latham and Inman, Lancet, London, 1908, ii, p. 1280.
[2] S. Solis Cohen, New York Med. Jour., January 20, 1912, p. 132; Critic and Guide, New York, April, 1913, p. 125.
[3] New York Med. Jour., 1913, xcviii, 268; Interstate Med. Jour., 1914, xxi, 297.

purum—similar reactions having since been observed with other preparations, as well.

As a result of these various lines of observation, the procedure now to be described was adopted, and has for some years been carried out.

I. *Preparation.* Observations were made with "old tuberculin (*O. T.*)," "tuberculinum purum (*T. P.* or *endotin*)," "bacillary emulsion (*B. E.*)," "bouillon filtrate (*B. F.*)" and "tubercle-bacilli residue (*T. R.*)." Latham had used T. R., giving it, by preference, with horse-serum, to promote absorption as well as effect, and this plan was followed at first in the hospital studies necessary to obtain familiarity with the workings of the remedy. When, however, the attempt was made to widen the scope of the work, and especially by entrusting the remedy to intelligent patients for use at home, the procedure was found to be too costly as well as too difficult. Tubercule-bacilli residue was therefore ground up with milk sugar, in such proportion that one gram of the powder contained one ten-thousandth of a milligram of the active substance. Thus a dose of 0.5 gram would contain one twenty-thousandth of a milligram of T. R., and a dose of 0.1 gram would contain one one-hundred-thousandth of a milligram of T. R., etc. This was given in diluted beef juice, whey, albumen water or skimmed milk (diluted) which answered equally as well as serum. Saline solution was used as the diluent, about half an ounce to an ounce of fluid (15 to 30 c.c.) being given altogether.

When experience had shown that very small doses and extremely minute increments were desirable, the manufacturers who had been kind enough to prepare the experimental powders (Messrs. H. K. Mulford Company) were asked to prepare a series of tablets varying in strength from one one-millionth of a milligram to one one-thousandth of a milligram each. These are now employed, and prove both convenient and efficacious.[1]

[1] In order to reduce the number of different strengths of tablets that druggists would have to carry in stock to meet prescriptions, the manufacturers have decided, after consultation with me, to market only two strengths: (*a*) one one-hundred-thousandth of a milligram, and (*b*) one one-thousandth of a milligram, respectively.

To administer a dose of one one-millionth of a milligram, tablet *A* should be dissolved in ten teaspoonfuls of water, one teaspoonful of which is to be added to the beef juice and the other nine thrown away. For any number of millionths

When smaller doses than one one-millionth of a milligram are desired, the tablet is dissolved in 1 c.c. or more of sterile water, and the appropriate number of drops added to the diluted beef juice, bouillon or other vehicle.

Similar tablets of O. T. and B. E. have also been made, and are available for cases in which these preparations are desirable.

When endotin is employed, the ampoules are used, the liquid contents being readily soluble in salt-water, beef juice, whey, broth, or horse serum for oral or rectal administration.

Dose. Latham had used one twenty-thousandth of a milligram of T. R. as his initial therapeutic dose in chronic cases, and the same quantity was used in the first observations at Philadelphia. Soon, however, it was found that in some instances distinct reaction occurred, even from so small a dose; or that, although reaction might not at first be marked, it became so after slight increase in the quantity administered. Accordingly, the initial dose was reduced to one one-hundred-thousandth of a milligram. In a number of cases, this proved to be entirely satisfactory, since it could be increased gradually, without the production of marked reaction, until a dose of one ten-thousandth of a milligram, or even one one-thousandth of a milligram, was reached. The observations already referred to, however, of subjective constitutional reaction from

up to nine, that number of teaspoonfuls is to be used and the balance thrown away. For doses in the hundred-thousandths up to ten, the tablet itself is available. For doses in the ten-thousandths, tablet *B* is to be dissolved in ten teaspoonfuls of water and the required number of ten-thousandths will be represented by the number of teaspoonfuls used. Since the cost of the tablets is largely in the making and not in the precise amount of tuberculin which they contain, this plan is no more expensive for the patient than the supply of tablets of the exact dose, while much more economical for the manufacturer and the dispensing druggist.

Of course, the powders containing a definite quantity of tuberculin product rubbed up with milk-sugar (say one ten-thousandth of a milligram to the gram) such as were used in the earlier observations, could be supplied, and a definite quantity of this dilution (still further diluted if necessary) divided extemporaneously, upon prescription, into any number of powders or triturates desired; but the objection to this method is that the thorough distribution and accurate subdivision necessary for precision in dose is difficult for the ordinary druggist not possessed of special machinery or especially expert in manipulation. I have followed this plan, however, with certain Philadelphia pharmacists willing to take the trouble, and it has been entirely satisfactory. Also a liquid preparation, such as is furnished for "serial dilution" for hypodermic injection can be used by the physician himself or a trained assistant for oral administration as well; but the dilution of this for a minute dose could not be entrusted to the patient or a member of the patient's household. It is purely a matter of convenience, and ready availability to use the tablets.

infinitesimal doses of tuberculinum purum, and a few instances of quite distinct reaction at one ten-thousandth of a milligram of T. R., even when the initial dose was but one-tenth of this, led to still greater modification of the dose. I now begin, as a rule, with one one-millionth of a milligram, and aim by gradual increase—not to produce reaction and then induce tolerance, but—if possible, to *avoid both objective and subjective reaction entirely.* According to circumstances, the dose is increased by one one-millionth of a milligram or less, at each repetition, until a dose of one one-hundred-thousandth of a milligram is reached—unless meanwhile there should be developed some of the subjective or objective symptoms of reaction—especially fever. In that case, the dose is diminished to the quantity previously tolerated and this is repeated twice before increase is again attempted.

At most, two doses of the tuberculin are given weekly, so that it may take four or five weeks or longer to reach the dose of one one-hundred-thousandth of a milligram. If this quantity is absolutely tolerated, the increment added to the successive doses may be augmented.

Here I have no fixed and invariable rule. Attempts have been made to work out an optimum proportional increase in percentages of the preceding dose, for the oral method, as by various observers for other methods; but this is supererogatory and troublesome. According to the time at one's disposal, the apparent severity of the case, and other factors—including tendency to reaction, and progressive improvement—the procedure must be individualized.

When the patient is tolerably robust, and there is no activity, or no great activity, of local phenomena—especially if softening and fever be absent, or at most only occasional rise of temperature exceeding 99.5° or 100° F. be manifested—one may justifiably risk increments of one two-hundred-thousandth of a milligram. This will at first be 50 per cent. of the preceding dose, then only 33.3 per cent. of the preceding dose, and so on, in diminishing ratio. If this increment of one two-hundred-thousandth milligram be well tolerated twice weekly, for a week or two, it may be raised to one one-hundred-thousandth. In the course of five to seven weeks

a dose of one ten-thousandth of a milligram will thus be reached; at which point a halt may well be made for several weeks. If, however, the patient is not robust, if there be tendency to fever, or if there be more than a few small or scattered liquid râles, *i. e.*, when tissue changes are, or recently have been, active, it is better to continue with minute increments—say one one-millionth or one five-hundred-thousandth of a milligram (*i. e.*, two one-millionths) even after reaching the one-hundred-thousandth milligram mark; or one may use three one-millionths or four one-millionths, according to circumstances. And the effect, toxic or remedial, of previous doses must always be taken into account. In other words, one must, as in any other medicinal procedure, "mix his (drugs) with brains."

In the manner indicated, avoiding reactive disturbance as much as possible, tolerance to increased quantities of tuberculin is slowly brought about, coincidently with improvement in both subjective and objective clinical phenomena. The dose of one ten-thousandth of a milligram is in some cases never exceeded. Should further increase seem to be necessary, however, the increment usually chosen, other things being equal, is one one-hundred-thousandth of a milligram. The increase is now made very slowly, the same dose being repeated for several weeks to a period of months, before increments as great as one ten-thousandth of a milligram are adopted. The maximum dose reached in nine-tenths of the cases thus far treated has been one one-thousandth of a milligram; but I do not hesitate to go up to one one-hundredth of a milligram, or even to a whole milligram, if in a particular case such advance of dosage should seem to be required. However, the good effects sought for are usually brought about by increases to maximal points between one ten-thousandth and one one-thousandth of a milligram and hence larger doses have not, as a rule, seemed either necessary or desirable.

If at any point in the course of treatment reaction is manifested, further increase is not attempted until the quantity producing the reaction has been tolerated at least twice; or should the dose which induced the reaction be more than two or three one-hundred-thousandths of a milligram, the usual, and I think the best, plan,

is to drop back to the dose previously tolerated, and to continue that quantity for two or three weeks before another attempt is made to secure tolerance of the increment. The more carefully one avoids even the slightest reactive disturbance, the more surely will the agent prove of therapeutic usefulness.

Frequency of Administration. Latham, Spitta and Inman say: "That T. R. is absorbed satisfactorily is shown by the fact that the smallest dose given in this investigation produced an immediate rise in the opsonic content of the blood. This dose was one twenty-thousandth of a milligram, which in reality represents one one-hundred-thousandth of a milligram, or one one-hundred-millionth of a gram. Administered in this way tuberculin stimulates the production of antibodies and so raises the opsonic content of the blood and confers immunity. The negative phase after absorption appears to be shorter and less marked when tuberculin is given in this way than it is when the hypodermic method is employed. Similarly, the positive phase has a shorter duration, and so far as this investigation has gone, seldom lasts more than five days. The positive phase, however, is often succeeded by a short negative phase and then by a more prolonged positive phase.

"Simultaneously with the improvement in the immunity curve produced by tuberculin occurs the improvement in the patient's condition. The temperature falls, the cough becomes less troublesome, expectoration is greatly diminished and the patient has a feeling of well being."

Myer Solis-Cohen and Albert Strickler,[1] studying the leukocytic picture, observed an increase in the lymphocytes and in the polymorphonuclear cells with one and two nuclei (the first two classes of Arneth) after the administration by mouth of old tuberculin (O. T.) and bouillon filtrate (B. F.).

Based upon these various observations, and with the object of avoiding negative phases and prolonging positive phases, I have in most cases adopted the plan of administering the tuberculin twice weekly; that is to say, after intervals of three and four days respectively. Indications in a particular case may, however,

[1] New York Med. Jour., 1912, xcv, 53.

point to the desirability of longer intervals, and in cases in which no therapeutic result is manifested, it is sometimes desirable to shorten the intervals in order to determine the degree of immunity, if any, that has been attained. Latham used both horse serum and physiological saline solution to promote absorption of the liquid preparation of T. R. that he employed. As a rule he gave the preference to horse serum, believing that this also possesses some desirable therapeutic property. As already stated, I have used diluted beef juice (pressed from raw meat or meat just "warmed" through), broth, whey, skimmed milk or albumen water, instead. I prefer the beef juice. Latham insists upon an empty stomach as the necessary condition for absorption of all "vaccines," and administers the tuberculin preferably before breakfast, believing the general resistance to be higher in the morning than in the evening. This is an excellent plan with bed patients, especially in febrile cases; and it may also be carried out when the patient, although not in bed, is at home, or at least, not occupied, during the day. Sometimes in the treatment of patients at their own homes, especially those who are able to work and are employed, it is better to give the tuberculin at night and have the patient remain in bed until noon of the next day; or later, should there be increase of temperature or other definite symptom of reaction. In this way, while observation of the effect of the agent cannot be so close, an undue loss of time from work is avoided. When the time comes that the patient can be allowed to walk about and work, even on the day he takes the tuberculin, either morning or evening may be chosen; or if the dose be given only once a week, as is frequent in such cases, the weekly day of rest offers the best time. It will thus be seen that it is necessary to individualize in each case, and to pay minute attention to all the details of environment, occupation and the like; but it is not necessary here to go into further elaboration on this head.

Duration. The treatment as a whole, is to be continued, with intermissions determined by results, for many months; and resumed from time to time, if necessary, over a period of many years. When resuming treatment after an intermission, the initial dose should be determined by the previous record of the patient. With-

out attempting to make a fixed mathematical rule, it has been my practice to resume with one-third to one-half of the maximum dose that was previously tolerated, and to increase with relative rapidity, provided the tuberculin continues to be well borne, up to that previous maximum. This quantity is then usually continued for some time without any further attempt to increase; but should progress not be satisfactory, a further slowly progressive increase is undertaken. Should the drug not be well borne, either it must be dropped or the dose reduced to a minimum and gradually increased, as in the first course.

SELECTION OF CASES. Here again we are chiefly indebted to Trudeau[1] for the establishment of correct principles. Without going further into history, or quoting varying opinions, it will suffice, for present purposes to indicate, as a result of personal observations and experience, those cases in which the general practitioner may, without fear, and with considerable benefit to the patient, institute the administration of tuberculin preparations by the mouth.

According to present knowledge, any preparation of the tubercle bacillus or its products is likely to do harm in the majority of what may be termed advanced, active cases. Nevertheless, there are some cases of this general group in which improvement, and even arrest of destructive processes, can be brought about by the cautious administration of one or another form of tuberculin. In my own experience, tuberculinum purum has been, in general, the most efficacious and the least provocative of reactive disturbance.

It is in these cases especially that Detre's method of control of tuberculin therapy by the "differential cutaneous reactions" may be of greatest service in selection of the particular agent to be employed.

However, the general practitioner should not attempt—at least for the present—to give tuberculin in these cases at all. In experienced hands, with the patient under continuous, skilled observation and complete control, it may be not only justifiable but desirable, to endeavor to prolong life or increase comfort by

[1] Loc. cit.

the judicious use of bacterial preparations. Under any other circumstances, the risk of doing harm and of hastening death outweighs the problematic chance of doing some good.

It is therefore only in comparatively early cases that I am at present prepared to recommend tuberculin for general use—and not in all of these.

In active—so-called acute—cases, with marked febrile movement and energetic tissue changes, I have, indeed, seen tuberculin do good; but only in skilled hands, with experienced attendants in charge of the patient, and all the circumstances of the environment under control. Such cases, therefore, are beyond the scope of the present paper.

In quite early cases of a sluggish, or at least inactive type, tuberculin is rarely needed. When suitable environment and proper food can be obtained, and when the physician is not afraid to use drugs judiciously—especially preparations of iodin (including the thyroid gland), of calcium, of arsenic and of iron—recovery will, in the vast preponderance of cases, take place without it.

Sometimes, however, even in the class of cases under consideration, those, namely, in which tissue changes have not progressed beyond the stage of infiltration and in which fever has not developed—improvement may be unduly slow, despite fresh air and good food, judicious regulation of exercise and rest, and the wise choice of medicaments. In another small group of cases, the improvement which sets in during the first few months of good treatment, may come to an abrupt standstill, considerably short of the point at which we can look for permanent recovery. In another, and still smaller, proportion of cases, not only will the improvement come to a standstill, but there may even be retrogression. Some tendency to febrile disturbance may be manifested; there will be loss of appetite, perhaps loss of weight; liquid râles may appear. In each of these three groups of cases—(1) those in which improvement does not begin quickly or progress with sufficient activity; (2) those in which improvement is prematurely arrested; and (3) those in which retrogression threatens or occurs—tuberculin employed with care and discretion will frequently prove of the utmost advantage.

In the first stages of its use the patient should be kept strictly at rest, especially in those cases which show liquefaction or a tendency to elevation of temperature. Afterward it may be necessary to keep the patient at rest only on the days when tuberculin is given, or that and the day following. Still later, when distinct improvement has set in and tolerance to the doses given has been secured, the patient may be allowed to move around as usual, even while taking the remedy.

It is particularly, however, in two other classes of cases that I have seen the best results from the use of tuberculin by the mouth.

Certain patients with chronic pulmonary tuberculosis, go along after the first months or years of improvement, (*a*) without definite recovery, or (*b*) with periods of relapse or recrudescence, in which there may be merely increase of cough, with perhaps slight hemoptysis, a limited area of fine râles, and an insignificant rise of temperature; or there may be days, or weeks, of considerable fever, marked activity in physical signs, and even invasion of new areas. The relapses may thus be very mild or quite severe.

Formerly, in my practice, these latter patients were treated in the following manner. Absolute rest was instituted so soon as symptoms of retrogression appeared, no matter how trifling, apparently, these symptoms might be—perhaps only the headache and malaise that come to be recognized as premonitory indications. Diet was regulated, ice applied over the heart if the temperature exceeded 99.8° F., perhaps the chest lightly blistered over the area of renewed liquefaction; and appropriate medicaments prescribed—usually creosote carbonate in rather full doses; sometimes digitalis, also in full doses; sometimes quinine hydrobromide, also in full doses. I now find that if, in addition, the administration of tuberculin be instituted and cautiously continued, improvement is more sure and more rapid than when tuberculin is not used. Care and caution are needed, however, in choosing the time and the dose, and in adjusting the increase of dose; and the maximal quantity reached is rarely so much as one ten-thousandth of a milligram. It is necessary, moreover, to observe the physical signs quite closely in order to make sure that the intensity of focal phenomena is not increased by the tuberculin. Quite often it is best to wait until the relapse

begins to show distinct signs of amelioration, or even until after recovery from the relapse—that is to say, until after the subsidence of the most acute symptoms. Tuberculin may then be given with intervals of from three to seven days between doses, and with cautious increase of quantity up to one ten-thousandth of a milligram—rarely beyond this—over a period of some months.

Accumulating experience tends to show that the tendency to relapse is thus greatly diminished, and in some cases apparently abolished; though of course, many years must elapse before a judgment of this kind can be considered final. Thus I well remember such a case, before the days in which I was willing to use tuberculin, in which eight years passed in apparent health, and then, following an indiscreet change of climate, a very severe and troublesome relapse set in. One should not be over-sanguine, therefore, in his statements or his expectations concerning patients of this group. Still there is sufficient evidence to warrant the opinion that tuberculin helps both to postpone relapses and to diminish their intensity and their duration.

As to those cases which simply "hang fire," as it were—neither recovering entirely nor losing much ground—tuberculin is of distinct service. It should be given say once or twice weekly, for three months or more; then intermitted for a month or two; then resumed; and so on over a period of years. Sometimes it clinches the recovery. Always it brings about marked improvement.

It will be seen, therefore, that tuberculin is advocated neither as a specific nor as a sole curative means, but simply as a slight *additional stimulus* to the natural defensive and recuperative processes of the organism—a little push to start them working in the beginning, or to send them on when they show lack of momentum—a little help to overcome unexpected obstacles or contrary forces that might even turn the wheels backward. And as too strong a push, or a push at the wrong time might upset the machine, one needs always to be careful and conservative in its application.

Case Records. Perhaps brief notes of a few typical cases will bring out more clearly, through concrete illustration, the chief points that have been set forth.

CASE I.—*Recurrent tuberculous peribronchitis. Recovery.*

H. D. Jr., now twenty-seven years of age, came under my care at the age of nine years. He was a thin, anemic, ill-developed child, with more or less constant cough and expectoration. Several members of his mother's family had died of tuberculosis, and a previous attendant had told his parents that he "would not live to be twelve years old." Physical examination showed scattered dulness throughout both lungs, especially marked along the borders of the sternum, and both fine and coarse crackling râles. He had fever (102° F.) when first seen, and for fourteen years, despite the marvelous general improvement resulting from hygienic and medicinal treatment, continued once or twice yearly to have brief relapses, attended with fever and with loss of flesh and strength. Profuse, fine râles would be heard, chiefly in the middle areas of the lungs and at the posterior bases—sometimes, however, at the apices. These attacks usually followed a period of prolonged fatigue from overwork or some indiscreet exposure. The young man, however, had grown tall, broad, and robust, weighed about 175 pounds, was a skilled swimmer and tennis player, and kept active in his outdoor occupation as assistant manager of a large estate. About four years ago, during a relapse in the summer time, I added to the usual treatment of rest and creosotal, the use of T. R. tablets by the mouth; beginning with one one-hundred-thousandth of a milligram and increasing to one twenty-thousandth of a milligram. The recovery was not much quicker than usual (taking about four weeks), but the recuperative tendencies were distinctly stimulated, so that the patient felt better during the attack than was the rule, and was stronger after it. The tuberculin treatment was continued for six months, with gradual increase of dose to one five-thousandth of a milligram; and then (active physical signs having been absent for five months) a somewhat rapid increase to one one-thousandth of a milligram was made for the purpose of provoking and overcoming febrile reaction. During this latter period, rest in bed was enforced on the "tuberculin days," once weekly. After one one-thousandth of a milligram could be borne without rise of temperature, a slightly smaller dose was continued once a week for three months longer. Since then there has been no relapse—this being the fourth year of exemption. However, tuberculin treatment was resumed every year except the present, for a period of two months, beginning, for convenience of notation, with the anniversary of the last attack. The dose used was one ten-thousandth milligram bi-weekly.

CASE II.—*Active early tuberculosis of lungs. Recovery.*

S. S., aged twenty-five years, traveling salesman, was first seen in the fall of 1909. He had had a distressing cough for three months or more, was losing flesh and strength rapidly, and had recently developed fever. His evening temperature was 102.2° F. ,the pulse rate varied around 120. There was scattered dulness, principally at the apices, with fine, dry râles

on the left and small moist râles on the right. He was put to bed in the open air (with an ice-bag to the precordium for an hour at a time, several times daily), and fed upon underdone, finely chopped beef, and hot water. Creosotal and tincture of digitalis were administered in ascending doses for effect. Later, slight blisters (one inch square) were made from time to time (one or two weekly) over the upper anterior chest, being allowed to dry without opening. The patient lost four pounds the first week, two pounds the second week, nothing the third week. In the fourth week he began to gain, and by the end of another month, fever and râles had disappeared, cough was markedly lessened, appetite was good, strength had begun to return, and there had been a net increase of twenty pounds in weight. Digitalis had been withdrawn and capsules of creosote and morrhuol were substituted for the creosotal. Improvement continued, although the patient was now permitted to move around. After some four months longer of treatment, during which "soluble" calcium lactophosphate (given in hot water an hour before meals) had been added to the medication, Mr. S. was allowed to work a few hours daily, calling upon city customers. The total net gain in weight at this time was thirty pounds; and the diet, while still consisting chiefly of rare broiled or roast beef and hot water, included also milk, eggs, rice, toast, butter, broths, fresh fruit, and green vegetables. In the course of some two months, occasional cough began to return, there was more or less malaise and some tendency to fever, with an impairment of appetite and a loss of five pounds in weight. Some moist sounds were heard at one apex. Rest was reinstituted, and the fever, râles and cough disappeared, but returned when the patient resumed moderate activity. Renewed rest was again followed by improvement, fever subsiding as before. Tuberculin residue was then given, the initial dose being one one-millionth of a milligram and the increase quite gradual. At one one-hundred-thousandth milligram, reaction was manifested by a slight rise of temperature (99.5° F.). Within twenty-four hours, however, the temperature fell to a point slightly subnormal. The same dose was repeated twice weekly for a month, without again causing fever. Cautious increase was now made, pausing or reducing the dose whenever the temperature rose, and then attempting to push on again to and beyond the reaction dose, until finally the patient became able to bear one one-thousandth of a milligram without the slightest febrile or other disturbance. During this time (some four months), rest, while not absolute and continuous, was fairly maintained; and complete rest was ordered not only on the day the tuberculin was given, but also on the following day, even when no reaction was observed. Whenever reaction occurred, the patient was kept absolutely quiet until it had passed over, and, as a rule, for forty-eight hours longer. After the dose of one one-thousandth of a milligram was tolerated several times in succession, the patient was permitted to move around, except on the day tuberculin was given, and the dose

was diminished to one two-thousandth of a milligram. This was kept up for a month longer. Tuberculin was then withdrawn for a month, to be resumed with an initial dose of one ten-thousandth of a milligram. For three years, the plan of taking the T. R. tablets once or twice weekly for a month, and then omitting them—at first for a month, later for two months—was followed pretty regularly. The patient was allowed to pursue his usual occupation all this time, except for absolute rest on the "tuberculin day." The tuberculin was then withdrawn altogether. The patient still remains well, fat, vigorous, and ruddy. I saw him so recently as a week before this account was written, and could find no evidence of pathological activity in the lungs.

CASE III.—*Advanced pulmonary tuberculosis with tendency to alternate quiescence and recrudescence. Prolongation of quiescent periods. Diminished severity of relapses.*

Mrs. S. P., was aged twenty-five years when she came under observation in 1907. Her father and sister had died of pulmonary tuberculosis and a brother of tuberculous meningitis. She had been coughing for some eighteen months, had been losing flesh during all that time, and had had fever and night sweats for three months. Menses had ceased, and the patient was quite anemic, a condition aggravated by recent hemorrhages. Tubercle bacilli were numerous in the sputum. There was considerable dulness over the lungs, chiefly apical on the left, and middle lobe on the right, but extensively distributed on both sides of the chest, both anteriorly and posteriorly. A fairly large, "active cavity" was evident in the middle portion of the superior lobe on the left. On the right there was a small apical cavity and numerous scattered, high-pitched liquid râles in other parts of the lung. Rest in the open air, and appropriate diet and medication (calcium, creosote, arsenic) were instituted. The patient rapidly improved, gaining considerable in strength, weight, and sense of well-being, and losing fever and sweats. The liquid râles disappeared, the cavities apparently became dry. In some six months there was recrudescence of activity, and after six or eight weeks, renewed improvement. This course continued for some three years, there always being a little further extension of tissue loss as a net result of each relapse. Tuberculin (O.T.) was then cautiously administered by the mouth, the patient being taken into a sanatorium for the purpose of close observation. The initial dose was one one-millionth of a milligram; the maximal dose reached during three months of absolute rest being one twenty-thousandth of a milligram. Improvement was steady and persistent. Calcium was continued, creosote and arsenic alternated, weekly, and tuberculin given once monthly in quantities cautiously increased to one ten-thousandth of a milligram. The patient is kept at complete rest the tuberculin day and the day following; but permitted to move around for half a day on other days. At one time staphylococcic and streptococcic bacterins were used additionally, to

combat the mixed infection. Tuberculinum purum and tubercle-bacilli residue have been tried in substitution for O. T., the effects appearing to be much the same whatever preparation is used.

The net result has not been to bring about recovery in this rather severe case, but to prolong the periods of quiescence and to lessen both the severity and the duration of the relapses. The comfort of the patient has been markedly increased, and I have no doubt that her life has already been greatly lengthened, and may last for several years more. Tuberculin is resumed and withdrawn and the dose varied from one twenty-thousandth to one one-thousandth milligram, according to the varying indications; and the same course is pursued in regard to arsenic, iron, and creosote. Calcium is kept up rather continuously. Blisters are applied from time to time.

It may be said, in conclusion, that Cases I and II illustrate fairly well the two groups of cases in which tuberculin may best be used by the general practitioner—always, however, with due care and caution. Case III illustrates a class of cases in which special experience, skilled nursing and favorable environment are necessary. To multiply instances would add nothing to the force of the illustrations, except perhaps to bring out some additional differences of detail in symptoms, progress and treatment, and thus emphasize once more the necessity for strict individualization in the management of each patient.

DISCUSSION

Dr. Abraham Jacobi. I have used the treatment described by Dr. Cohen in a small number of cases. I have not seen any unfavorable or unpleasant symptoms from that use of tuberculin. I have used it in doses of from one hundred-thousandth of a milligram up to one five-thousandth of a milligram, and I must say I have never seen increase in temperature, or any unpleasant symptom that I could attribute to the tuberculin. I have given it in combination with other treatments. My routine treatment of these chronic cases of tuberculosis consists of the internal administration of guaiacol and arsenic. I never, in these chronic cases, undertake treatment without the use of those remedies.

MITRAL STENOSIS: OBSERVATIONS ON 200 CASES, BEFORE AND AFTER DEATH. ALSO ON 116 CASES NOT AUTOPSIED

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The study of 200 autopsied cases of mitral stenosis and 116 cases not autopsied forms the material for this presentation. Of the 200 autopsied cases, 130 died at the Massachusetts General Hospital[1] and 70 at the Boston City Hospital.[2] 50 of the latter have already been studied and reported on by Dr. George G. Sears, in the *St. Paul Medical Journal*, 1907, vol. ix, p. 135; but he has generously permitted me to go over the records once more and to add them to this study. The general statistics of these cases are shown in Table I.

Table I.

M. G. H. 130 autopsies (1892–1914).

Pure mitral stenosis[3]		93 or 71 per cent.
Mitral and aortic stenosis	21	
Mitral and tricuspid stenosis	4	37
Mitral, aortic, and tricuspid stenosis	9	
Mitral, aortic, tricuspid, and pulmonary stenosis	3	
		130

B. C. H. 70 autopsies (1896–1912).

Pure mitral stenosis	58 or 82 per cent.
Mitral and aortic stenosis	7
Mitral, aortic, and tricuspid stenosis	5
	70

M. G. H. and B. C. H. 200 autopsies.

Pure mitral stenosis	151 or 75 per cent.
Mitral and aortic stenosis	28
Mitral, aortic, and tricuspid stenosis	14
Mitral and tricuspid stenosis	4
All valves stenosed	3
	200

[1] Abbreviated to M. G. H. in tables and elsewhere.
[2] Abbreviated to B. C. H. in tables and elsewhere.
[3] For example, unassociated with lesions of other valves. I do not intend to exclude a concomitant mitral regurgitation.

I am somewhat surprised to find so large a proportion of cases, showing what I have here called "pure mitral disease," *i. e.*, mitral stenosis without any marked involvement of the other valves. The phrase "pure mitral stenosis" is *not* used to exclude a concomitant mitral regurgitation. In several of the cases which I have called "pure" there was also some fibrous thickening of the aortic or of the tricuspid, but probably not sufficient to injure the function of the valves.

In the study of these cases I have not been content with copying the anatomical diagnoses from the autopsy records, but have read in detail the careful descriptions written by Dr. Frank D. Mallory, Pathologist of the Boston City Hospital, by Dr. James H. Wright, pathologist of the Massachusetts General Hospital, and Dr. Oscar Richardson, assistant pathologist of the same institution. To these gentlemen, for their unvarying courtesy and kindness in explaining and interpreting records, I owe a great debt. But for their skilful and faithful work, preserved in their records freely opened to me for study, this paper would have been wholly impossible.

TABLE II.—Age.

	(*a*) Autopsied cases.		(*b*) Non-autopsied cases.
	M. G. H.	B. C. H.	M. G. H.
0 to 10	1	1	2
11 to 20	12	2	14
21 to 30	26	12	27
31 to 40	32	19	43
41 to 50	21	18	20
51 to 60	24	7	8
61 to 70	11	6	2
71 to 80	3	2	0
Age in doubt	0	3	0
Totals	130	70	116

AGE. In Table II the statistics of the patients' ages are recorded. In the cases autopsied at the Massachusetts General Hospital it will be noticed that although the largest number falls in the decade between thirty and forty, there is a secondary rise in the number of persons dying during the years between fifty and seventy. Comparison of the columns of autopsied cases with those not autopsied shows that in the latter there is no such rise during the later years. I interpret this discrepancy to mean that it is especially in the elderly patients that the diagnosis of stenosis at the mitral is most

often missed. Additional reasons for this belief will be given in the section on diagnosis.

The data as to age, collected in Table II, refer, of course, to the age of the patient at the time when the disease was recognized, not to his age at the time when the disease began. Table III shows the age at which the patient first suffered from rheumatism, chorea, or heart symptoms. From this table it appears that at the Massachusetts General Hospital 43 per cent. of all cases probably began before the twenty-first year and 83 per cent. before the thirty-first year. At the Boston City Hospital the figures are practically identical, 81 per cent. of cases beginning before the thirty-first year.

TABLE III.—One Hundred and Twenty-five Autopsied Cases. Age at which the patient first suffered from rheumatism, chorea, or cardiac symptoms.

M. G. H.			B. C. H.		
0 to 5	1	72 or 83 per cent. before the thirty-first year.			
6 to 10	11		0 to 10	5	31 or 81 per cent. before the thirty-first year.
11 to 15	14				
16 to 20	17		11 to 20	7	
21 to 25	11				
26 to 30	18		21 to 30	19	
31 to 35	7				
36 to 40	6		31 to 40	7	
41 to 45	2				
			41 to 50	0	
Total	87		Total	38	

Tabe IV shows the total duration of the same group of cases so far as it can be estimated. It substantiates the opinion long current, that if a patient with endocarditis of the mitral valve gets by his twenty-first year, and especially if he gets by his thirtieth year, without succumbing to an attack of acute endocarditis his trouble is likely to settle down into a form quite compatible with many years of life and often with complete functional activity.

TABLE IV.—Total Duration of these Cases Since First Symptoms of Rheumatism, Chorea, or Endocarditis.

	M. G. H.	B. C. H.
0 to 5 years	15	15
6 to 10 years	23	6
11 to 15 years	11	5
16 to 20 years	10	5
21 to 25 years	11	1
26 to 30 years	1	4
31 to 35 years	5	2
36 to 40 years	1	0
Totals	77	38

A comparison of Table II and Table V shows that the cases which begin insidiously, without any known date, without any obvious affection of the joints (rheumatism), of the nervous system (chorea), or of the blood-stream (general septic infection), live much longer than those which begin in the ordinary way, with symptoms of rheumatism, chorea, or endocarditis.

TABLE V.—Age of Death in Cases Without Known Cause or Date of Beginning.

	M. G. H.	B. C. H.
21 to 30 years	1	0
31 to 40 years	4	5
41 to 50 years	10	10
51 to 60 years	16	4
61 to 70 years	9	7
71 to 80 years	3	2
Totals	43	28

TABLE VI.—Sex.

(*a*) In autopsied cases at M. G. H.: male, 62; female, 68
(*b*) In autopsied cases at B. C. H.: male, 29; female, 41

Total autopsied cases: male. 91; female,109
(*c*) Non-autopsied cases: male, 41; female, 75.
(*d*) Pure mitral stenosis:
  (*a*) Autopsied cases: male, 64; female. 87.
  (*b*) Non-autopsied cases: male, 32; female, 66.

SEX (see Table VI). There was a slight excess of females among the autopsied cases; 109 females to 91 males; or 54.5 per cent. of females to 45.5 per cent. of males. In the Massachusetts Hospital autopsies the difference was very slight, 62 males to 68 females. At the Boston City Hospital there was a wider discrepancy, 29 males to 41 females, or 58+ per cent. of females to 42− per cent. of males. In the non-autopsied the preponderance of females was greater, 75 females to 41 males. This means that 64 per cent. in the non-autopsied cases were in women. If we divide the cases into those of "pure mitral stenosis," on the one hand, and those of mitral stenosis with other valve lesions, on the other, it appears that in the latter group (the complicated cases) there was a slight excess of *males*, 27 males to 22 females, while in the autopsied cases of "*pure*" mitral stenosis there were 87 females to 64 males. In the non-autopsied cases of pure mitral stenosis the figures are about the same, 56 females to 33 males.

To me the surprising thing in these figures is that the predominance of females is not more striking, since it is well known that the number of cases of chorea and of acute rheumatism is very much larger among females than among males.

Etiology. Table VII lists the more important figures relating to etiology, *i. e.*, those relating to chorea and acute rheumatism. No other infection occurred frequently enough to be of any considerable importance as it seems to me, but for the sake of completeness I add here, in Tables VIII, IX, and X, all the known facts.

Table VII.—Rheumatism or Chorea.

Autopsied cases:	M. G. H.:	71 out of 110 questioned (64%)
Autopsied cases:	B. C. H.:	27 out of 48 questioned (56%)
Non-autopsied cases:	M. G. H.:	50 out of 83 questioned (60%)

Table VIII.—Massachusetts General Hospital. One Hundred and Thirty Autopsied Cases.

Other infectious diseases were not often carefully inquired about. The following items were recorded but have little to show:

Pneumonia[1]	21	Grippe	3
Purpura	8	Diphtheria	4
"Sore throat"	6	Measles	2
Tonsillitis	4	Mumps	1
Bronchitis	2	Ulcer of palate	1 (syphilis)

Table IX.—Massachusetts General Hospital. One Hundred and Sixteen Non-autopsied Cases.

Pneumonia	17 cases.
Tuberculosis	1 "
Purpura	1 "
Tonsillitis	4 "
"Sore throat"	3 "
Colds	2 "
Bronchitis	5 "
Scarlet fever	32 "
Measles	24 "
Diphtheria	16 "
Chicken-pox	2 "
Smallpox	5 "
Chancre	3 "
Yellow fever	2 "
Malaria	3 "
Whooping cough	6 "
Typhoid	11 "
Grippe	9 "
Mumps	13 "
Favus	1 "
Gonorrhea	3 "

[1] 18 lobar pneumonia; 3 bronchopneumonia.

TABLE X.—Boston City Hospital. Seventy Autopsied Cases.

Pneumonia (3 lobar, 4 broncho-, 2 [?])	9 cases.
Tuberculosis (healed)	1 "
Purpura	3 "
Tonsillitis	3 "
Peritonitis	1 "
Erysipelas	1 "

All the evidence tends to show that no infection except the form of streptococcosis manifested in rheumatism and chorea and in "primary" acute endocarditis bears any known relation to mitral stenosis.

In studying the hearts of elderly persons dying of mitral stenosis, it is often hard to be sure whether or not arteriosclerosis bears a relation to the disease, but the weight of evidence is, I think, against any such belief.

DIAGNOSIS. Table XI expresses in rather humiliating figures our successes and failures in diagnosis. These figures sharpen the point already made earlier in this paper, namely, that the cases of mitral stenosis which arise insidiously are likely to live to a considerable age and are much more apt to be missed in physical examination.

TABLE XI.—Diagnosis of Mitral Stenosis Made.

At M. G. H. in 73 out of 130	56 per cent.
At B. C. H. in 36 out of 70	51 per cent.

75 per cent. of the correct diagnoses were in rheumatic patients under 40.
70 per cent. of the wrong diagnoses were in non-rheumatic patients over 40.

Clinically we may divide cases of mitral stenosis into four groups:

1. Those that first come to the physician's notice with symptoms of *infection*.

2. Those first disabled by *"cardiac symptoms,"* such as dyspnea, palpitation, or edema.

3. Those in which the first manifestations are *embolic* (hemiplegia, embolism of an extremity, mesenteric embolism).

4. Those which present *no symptoms* whatever during life, but are found postmortem in patients who have died of some other disease.

It seems to me worth while to illustrate this clinical grouping rather copiously and to marshal the main facts regarding the mode of onset.

TABLE XII.—Massachusetts General Hospital. One Hundred Autopsied Cases of Mitral Stenosis, "Pure" or Complicated by Lesions of Other Valves.

FIRST SYMPTOM WAS	
Dyspnea (30 in "pure," 14 in complicated cases)	44
Infection	11
Coma	6
Cough	5
Pain and coldness in one or both feet	5
Edema	4
Hemiplegia	3
Palpitation	3
Ascites (2 in complicated cases)	3
Weakness	3
"Run down"	3
Joint pains	2
Pain, substernal	2
Pain, umbilical	1
"Collapse"	1
Epistaxis	1
Nausea and vomiting	1
Aphasia	1
Pain in right hypochondrium	1
Total	100
Cardiac	61
Infectious	13
Embolic	14
Miscellaneous	12
Total	100

TABLE XIII.—Massachusetts General Hospital in Ninety-seven Cases of Mitral Stenosis Not Autopsied.

FIRST SYMPTOM WAS	
Dyspnea	29
Infection	14
Hemiplegia 6, aphasia 2, coma 2	10
Cough	8
Palpitation	7
Joint pains	5
No symptoms at all (accidentally found)	5
Weakness	4
Diarrhea	4
Chill	3
Vomiting	3
Edema	2
Hemoptysis	1
Pain in chest	1
Pain in right hypochondrium	1
Total	97
Cardiac	48
Infections	22
Embolic	10
Miscellaneous	17
Total	97

The symptoms first complained of are shown in Tables XII and XIII. The autopsy statistics show that while a majority (61 per cent.) of all cases begin in the traditional way with dyspnea, cough, palpitation, or edema, there are 27 per cent., an interesting minority, especially numerous among the cases of uncomplicated mitral stenosis, in which the extracardiac symptoms dominate the clinical picture.

Among the 100 cases autopsied at the Massachusetts General Hospital one of the "cardiac" or "mechanical" group of symptoms (dyspnea, cough, substernal pain, palpitation, edema, ascites) was the first to appear in 61 cases.

The "infection group" of symptoms (*i. e.*, fever, chill, joint pains, etc.) appeared first in 13 cases.

The "embolic group" (hemiplegia, aphasia, peripheral embolism, coma) appeared "out of a clear sky" in 14 cases.

Other symptoms less easily classified are listed in Table XII.

I will quote next some of the history notes of these cases.

INFECTIOUS TYPE

In Case 68 of the series of autopsies in the Massachusetts General Hospital (autopsy 520) the patient entered the hospital after a week's illness, beginning with a chill, precordial pain, a temperature of 102, and a leukocytosis of 26,000. Nevertheless, at autopsy, three days later, there was no evidence of acute infection anywhere and blood-cultures remained sterile. There was a ball thrombus to the left auricular appendage, but without any evident embolism. It is hard to see how the acute symptoms are to be accounted for.

In Case 64 (autopsy 671) the patient had been perfectly well until five weeks from the date of the autopsy. The first symptom was a local sepsis of the arm, without any known point of entry. A week after its infection the arm was opened, but three weeks later the wound was still unhealed. Eight days before death there was a chill, with headache, general body pains, severe pain in the right knee, and marked general prostration. The wound looked healthy and there were no cardiac symptoms at any time. During the five days of hospital observation preceding death, there was continuous fever, averaging 104°, though the leukocyte counts

(four in number) ranged between 6000 to 8000. At autopsy an acute endocarditis was found, *superimposed upon a chronic process in the mitral valve;* an acute process, also, on the aortic valve. Blood-cultures showed a streptococcus the precise nature of which was not further studied. There was also a localized fibrinopurulent peritonitis without any obvious perforation of any abdominal organ. The point of interest here is the finding at autopsy of a *chronic* endocarditis as well as an acute process, though all the patient's symptoms were attributable to the latter. A similar state of things was found in eleven other cases, of which the foregoing may be taken as a sample.

In Case 46 (autopsy 1182) the patient began to feel "run down" four weeks before entering the hospital. He had had no previous illness of any kind and had never suffered from tonsililtis, rheumatism, or chorea. Three weeks before entering the hospial he began to have attacks starting with the sense of a lump rising in his throat. Soon after this he would feel choked, would gasp for breath, and get blue in the face. The whole attack came on with great suddenness, lasted two or three hours, and then subsided, leaving him perfectly well. Such attacks always came in the late afternoon or evening and seemed to be brought on by exertion or excitement. This patient lived a month in the hospital, and until ten days before his death showed pure cardiac symptoms, *i. e.*, those ordinarily associated with failing compensation. Ten days before death erysipelas developed. At autopsy blood-culture showed a streptococcus, but there was no other evidence of acute infection; the heart lesions were all of chronic type.

In Case 73 (autopsy 335), a woman, aged thirty-two years, had been well until the birth of a child, four months ago. Since then she had been poorly, expecially during the past two weeks. Five days before entering the hospital, menstruation began for the first time since parturition. On the day before entrance she was seized with precordial pain and cough. She lived but two days in the hospital, the symptoms being mostly those of a failing heart, no fever or leukocytosis, though purpuric spots were scattered over the chest and abdomen. Autopsy showed acute and chronic endocarditis with acute glomerulonephritis.

EMBOLIC TYPE

Cases beginning with symptoms of embolism, which appear "out of a clear sky," are of special interest because the diagnosis is so often missed. In Case 56 (autopsy 1008), a woman, aged fifty-four years, who had never previously been sick in her life, gave the following history: Two weeks ago she was wakened in the night by severe pain in the right hypochondrium, with vomiting. In a few hours the pain was gone and she felt well until eight days ago, when she was attacked as before, but now the pain continued with varying severity and with daily vomiting, up to the time of her hospital entrance. There were no cardiac symptoms of any kind. Physical examination showed marked tenderness and resistance in the right lower quadrant of the abdomen. During the four days of her hospital life there was continuous fever, gradually rising from 102° to 106°. The leukocyte count averaged 24,000. No cardiac murmurs were detected. The heart was not enlarged. There was no cyanosis or evidence of passive congestion anywhere. The pulse was very irregular, of small volume and low tension. At autopsy there was a well-marked mitral stenosis, the valve 5 cm. in circumference. There was a thrombus in the left auricular appendage and several branches of the superior mesenteric artery were plugged, with a resulting infarction of the intestine and general peritonitis. The endocarditis was of a chronic fibrous type, without any acute inflammation.

In Case 62 (autopsy 683), a woman, aged twenty-nine years, who had had rheumatism in childhood, but no cardiac symptoms of any kind, noticed six days before entering the hospital that her right foot was paralyzed, numb, white, and cold. A few hours later severe pain began. This has persisted ever since. Three days ago the skin of the lower leg began to be discolored. The patient entered the surgical wards for amputation. Nothing wrong was detected there as regards the heart, except that the pulse was very irregular in force and rhythm. The patient died after fifteen days' stay in the hospital. During that period she had fever which began immediately after the operation, and gradually rose to 103° at the time of death. The leukocyte count was 21,000 at entrance.

Autopsy showed a mitral valve measuring only 4 cm. in circumference, a thrombus in the left auricular appendage, and an embolism of the right external iliac artery. There was no acute endocarditis, and no infection of the blood-stream.

Case 63 (autopsy 861), a woman aged sixty years, who had never been sick before in her life, was seized seventeen days ago with cramp and numbness in both lower limbs. The right leg improved in a few days, but the left foot went on to gangrene and had to be amputated. Later the right foot became gangrenous and was amputated. On the day before death she developed a "right hemiplegia." In the surgical wards where this patient was treated, nothing wrong was found with the heart. At autopsy the mitral valve measured 5 cm. in circumference. There was thrombosis of the left auricular appendage, of the right axillary artery, and of the common iliac artery on each side. A streptococcus was cultivated from the heart's blood.

Case 118 (autopsy 1249), a woman, aged forty-eight years, who had never been sick in her life, was seized on the day before entering the hospital with agonizing pain in the abdomen, associated with nausea, vomiting, and diarrhea. The abdomen was opened at once for acute intestinal obstruction and showed thrombosis of the superior mesenteric vein, with infarction of the jejunum. The patient died next day. Autopsy showed, strange to say, no thrombosis of the left auricular appendage. The mitral valve measured 7 cm. in circumference, but showed no acute endocarditis. Blood-cultures remained sterile.

In Case 20 of the series not autopsied, a woman, aged forty-nine years, previously in perfect health, was seized a month before entrance with severe pain in the right upper quadrant, lasting twelve hours, followed by vomiting, vertigo, dyspnea, and palpitation. While in the hospital this patient showed all the usual signs of mitral stenosis with no evidence of infection and nothing to suggest embolism, unless the attack above described is to be interpreted as embolic. Physical examination showed tenderness in the right hypochondrium and the liver edge was palpable 3 cm. below the ribs, but after a few days' rest in bed all symptoms disappeared and the patient left in good condition. Just what the nature of this

attack was I am unable to say. It reminds us of Case 56 above reported (mesenteric embolism).

In Case 48 of the same series, a woman, aged forty-four years, previously quite well, was seized just one year previous to entrance with coma lasting four hours, followed by right hemiplegia. In the year following this there was gradual improvement, but she is still unable to move the right leg. This patient had never had any cardiac symptoms and came to the hospital for the relief of the paralysis. Physical examination showed all the ordinary signs of mitral stenosis.

With this obvously embolic case may be contrasted some less clearly defined: Case 81 of the series not autopsied occurred in a man, aged thirty-six years, always free from cardiac symptoms and from all manifestations of rheumatism or chorea, although since his fifteenth year he has had a good deal of muscular twitching after any hard work or excitement. January 27, February 5, and March 8, 1904, he had sudden attacks of coma lasting about fifteen minutes. He entered the hospital on March 8, and in the ward had almost daily attacks of vertigo and faintness without loss of consciousness. During several of these attacks the pulse was very rapid and irregular. There was no evidence of any acute infection. The heart showed all the usual evidences of mitral stenosis. He left the hospital in three weeks slightly relieved.

In Case 9 of this series, a man, aged thirty-eight years, who had never had any evidences of disease, gave the following history: Eighteen days ago, while cooking his breakfast, he suddenly became stiff and would have fallen if he had not been caught by his companion. His mouth was pulled to one side and his jaw was tightly set. There were no clonic movements. Muscular rigidity passed off in an hour, but was followed by an aphasia lasting two days. After that there was gradual improvement, so that at the present time he has very little difficulty with his speech. On examination he showed no aphasia or paralysis; there were all the usual signs of mitral stenosis.

Case 16 of this series was, like the previous case in that the patient had never had any previous illness nor any symptom referable to the heart. Six days before entrance he suddenly noticed that he

could not talk or whistle and that the right side of his face would not work. He was brought to the hospital on account of the aphasia and left in a week without any improvement. Two weeks later he came back again on account of headache and indigestion. His aphasia was now somewhat improved, but still troubled him a good deal. The headache and indigestion disappeared in a few days. Besides the aphasia there was at this time a slight hemiparesis on the right side, with absence of peripheral reflexes on that side. Though the heart showed good evidence of mitral stenosis there was at no time any symptom of infection or of failing compensation; the symptoms were purely embolic.

TABLE XIV.—Heart Weights in Pure Mitral Disease.

	M. G. H.	B. C. H.
Under 300 grams	9	11
301 to 400 grams	24	17
401 to 500 grams	27	20
501 to 600 grams	20	6
601 to 700 grams	5	2
701 to 800 grams	4	0
Totals	89	56

Over 400, 84 or 60 per cent.; in 88 per cent. of all cases the heart was considered by pathologist to be enlarged.

TABLE XV.—Left Ventricle in Pure Mitral Disease, M.G.H., 81 cases.

10 mm. or less in	25 or 30 per cent.
11 to 14 mm. in	32 or 40 per cent.
14 mm. or more in	24 or 30 per cent.
Total	81

TABLE XVI.—Right Ventricle in Pure Mitral Disease, M.G.H., 76 cases.

3 mm.	15
4 mm.	23
5 mm.	19
6 mm.	8
7 mm.	5
8 mm.	5
9 mm.	1
Total	76

THE SIZE OF THE HEART AND OF THE VENTRICLES. In Table XIV are shown the weights of the hearts in cases autopsied at the Massachusetts General Hospital and at the Boston City Hospital. Tables XV and XVI show the thickness of the left ventricle and of the

right ventricle as listed in all the cases in which careful measurements were taken. In a general way these tables show that the heart is enlarged in nine-tenths of the cases of mitral stenosis and that this enlargement is often very considerable. The enlargement includes all parts of the heart and is by no means confined to the right ventricle. Atrophy of the left ventricle is mentioned in only two cases.

These figures correspond with the observations made during life regarding the size of the heart. Table XVII shows that in 26 out of 63 cases there was a considerable enlargement of the heart downward as well as outward; in other words, an enlargement of the type often associated with left ventricular hypertrophy. These, it should be remembered, are cases of pure mitral stenosis. It is clear, therefore, that in differential diagnosis one cannot rule out pure mitral stenosis merely because there is good evidence of left ventricular hypertrophy.

TABLE XVII.—In Sixty-three Cases of Pure Mitral Stenosis the Cardiac Apex extended to the

5th interspace in or within nipple line in	12 cases at M. G. H.
5th interspace outside the nipple line in	25 cases at M. G. H.
6th interspace outside the nipple line in	20 cases at M. G. H.
7th interspace outside the nipple line in	5 cases at M. G. H.
8th interspace outside the nipple line in	1 case at M. G. H.
Total	63

ADHERENT PERICARDIUM AS A COMPLICATION

Seven out of the seventy cases of mitral stenosis autopsied at the Boston City Hospital were found to be associated with adherent pericardium. In these cases the heart weights were as follows:

260 grams	480 grams
310 "	490 "
403 "	560 "
440 "	

The average weight, as will be seen, is not appreciably greater than in cases of pure mitral stenosis without pericarditis.

At the Massachusetts General Hospital there were 19 out of 120

cases of pure mitral disease associated with chronic adhesive pericarditis. The weights of these hearts were as follows:

290 grams	486 grams
300 "	509 "
319 "	510 "
325 "	520 "
352 "	528 "
386 "	560 "
387 "	565 "
420 "	640 "
457 "	739 "

In the last case (739 grams) there was subacute glomerulonephritis in addition. In one case the heart was not weighed. Obviously, these hearts, unlike those weighed at the Boston City Hospital, averaged heavier than those of pure mitral disease alone.

NEPHRITIS AS A COMPLICATION

Table XVIII shows the weights of 20 out of 70 cases autopsied at the Boston City Hospital. In these cases there was pure mitral stenosis associated with some type of nephritis. Only ten of these weighed more than 400 grams.

TABLE XVIII.—Boston City Hospital. Weight of Heart with Pure Mitral Plus "Nephritis."

175 grams	403 grams
190 "	420 "
235 "	420 "
320 "	435 "
340 "	435 "
340 "	440 "
355 "	517 "
372 "	555 "
385 "	575 "
390 "	685 "

20 cases (out of 70).

In 20 out of 120 cases autopsied at the Massachusetts General Hospital there was an association of pure mitral stenosis with nephritis. In all but one case the nephritis was of a subacute or chronic type. The weights of the hearts in these cases were as follows:

252 grams	472 grams
291 "	550 "
312 "	565 "
320 "	570 "
328 "	600 "
340 "	648 "
386 "	648 "
403 "	710 "
435 "	739 "
	750 "

One heart was not weighed.

Here again some increase in weight attributable to the nephritis is obvious.

In the case of combined valvular lesions the heart weights were considerably greater than those in pure mitral stenosis. When mitral disease was associated with aortic stenosis the average weight of the heart was 650 grams. When mitral disease was associated with tricuspid stenosis the hearts averaged 507 grams in weight.

AUSCULTATORY SIGNS

The most important point, as I see it, in these cases, is the presence of soft early-diastolic murmurs along the left sternal margin in 22 out of 50 autopsied cases in which such murmurs were listened for. These murmurs were distinguished from the low-pitched, vibrating presystolic or diastolic roll, ordinarily heard in the vicinity of the cardiac apex. The murmurs to which I am now inviting attention were of the soft-blowing type such as is ordinarily associated with aortic regurgitation and such as have been explained by Graham Steele as due to high pressure in the pulmonary artery. Postmortem the hearts of these patients showed no recognizable lesion of the aortic or pulmonary valves and no dilatation of the pulmonary artery. The importance of such murmurs is due to the fact that they make more difficult our differentiation of aortic from mitral disease.[1]

In pure aortic regurgitation we often have a diastolic murmur like that above described and in addition a presystolic murmur, the so-called Austin Flint murmur, at the apex. It now appears that *in pure mitral stenosis we often have exactly this same combination of murmurs*, namely, a presystolic at the apex and a soft diastolic along the left sternal margin. This is very confusing, especially as clinical evidences of left ventricular hypertrophy have been shown in the figures quoted above to be present in no inconsiderable proportion

[1] Mackenzie (Diseases of the Heart, 1913) makes no mention of such murmurs. He refers only to a "diastolic diminuendo murmur heard only in the immediate vicinity of the apex beat." John Cowan (Diseases of the Heart, 1914) mentions a murmur like that which I am describing, but refers it to dilatation of the pulmonary artery.

of the cases of pure mitral stenosis. In such cases, so far as I can see, the diagnosis must rest upon the phenomena present in the peripheral arteries (Corrigan pulse, capillary pulse, etc.), and especially upon the nature of the infection underlying the whole process. If there is good evidence of a previous rheumatism we have more reason to incriminate the mitral valve. If we have good evidence of syphilis, the aortic valve is under suspicion.

Presystolic murmurs were detected in but 58 out of 81 cases autopsied at the Massachusetts General Hospital. In the remainder of the 130 cases of this series the record is incomplete. Such murmurs were heard with about equal frequency in the cases of "pure mitral stenosis" and in those complicated by stenosis at one of the other valve orifices. Thus in the pure mitral cases presystolic murmurs were present in 40 and absent in 19. In the cases of multiple valve lesion this murmur was present in 18, absent in 4. In the 116 non-autopsied cases studied at the Massachusetts General Hospital presystolic murmurs were heard in 115.

Systolic murmurs were present in this same series in 94 cases, and absent in 15. In 21 cases there was no sufficient record. In the "pure mitral" cases this murmur was present 64 times and absent 13 times. In those complicated by aortic or tricuspid lesions, systolic murmurs were present 30 times, absent twice. The appearance of systolic murmurs in the non-autopsied cases is about the same: present 52, absent 8, no record in the remainder.

In the Boston City Hospital autopsied series, systolic murmurs were detected in 32 out of 42 of the pure mitral cases, and in 11 out of 12 cases of the more complicated valve lesions. Presystolic murmurs were heard in the Boston City Hospital series in 24 out of 35 pure mitral cases and in 4 out of 6 complicated.

A reduplication of the second sound was noted eighteen times in the non-autopsied series. In the autopsied cases the observations upon these points were not sufficiently numerous to be of value.

Sharpness of the First Sound. (Massachusetts General Hospital autopsied cases.) This sign was noticed in 17 out of 29 cases of pure mitral stenosis and 9 out of 12 in cases by other valve lesions.

Palpable thrill was present in 31 out of 35 cases of "pure mitral stenosis" autopsied at the Massachusetts General Hospital and in

13 out of 15 cases of combined valve lesions in the same series. At the Boston City Hospital a thrill was felt in 23 out of 29 cases in which attention was directed to this point. In the non-autopsied cases at the Massachusetts General Hospital a thrill was present in 89 out of 116.

FEVER

In Table XIX the number of cases showing fever in each of the three series referred to throughout this paper is shown. Fever is present in about 60 per cent. of cases, and is slightly more common in the cases with multiple valve lesions than in those with one only. It is striking how much more frequent fever is in the autopsied cases than in those not autopsied. I take these figures to mean that the terminal attack is usually an infectious process, whereas the milder attacks (non-autopsied cases) from which the patient recovers are more often wholly or partly mechanical. In other words, their symptoms are more like what has been generally associated with a failure of compensation.

TABLE XIX.—Fever.

	Pure mitral.		Cases complicated with other valve lesions.	
	Fever.	No fever.	Fever.	No fever.
M. G. H. autopsied series	47	27	31	17
B. C. H. autopsied series	19	10	7	0
M. G. H. series not autopsied	21	75	8	8

Chills were not frequent in this series. Their presence is recorded in only 7 out of 70 cases autopsied at the Boston City Hospital, and although their absence is definitely reported only five times, it does not seem to be likely that all mention of them would have been omitted had they been frequently present.

Leukocytosis was present in 61 out of 93 cases autopsied at the Massachusetts General Hospital. There was no difference in the counts of "pure" or "complicated" cases. (See Table XX.)

Anemia was present in 22 out of 81 cases autopsied at the Massachusetts General Hospital and in 25 of 103 among those not autopsied. I have called any case anemic in which the hemoglobin percentage was 75 or less.

Albumin and casts were present in 107 of the autopsied cases. Albumin without casts in 19. On the other hand, in the cases not

autopsied, albumin with casts was present only 33 times and albumin without casts 13 times. In both series the cases with several valve lesions show a higher percentage of albuminuria and casts.

TABLE XX.—Leukocytosis in One Hundred and Twenty M. G. H. Autopsied Cases.

	Pure mitral.	Complicated.
"No leukocytosis"	8	3
10,000 or under	14	7
11,000 to 13,000	8	3
14,000 to 15,000	9	4
17,000 to 20,000	5	0
21,000 to 30,000	8	4
31,000 to 55,000	1	1
"Leukocytosis"	12	6
	65	28
No record	22	5
	87	33

Leukocytes increased (11,000 or more) in 43 of 65 "pure" cases, or 66 per cent.
Leukocytes increased (11,000 or more) in 18 of 28 "pure" cases, or 64 per cent.

Absolute Arhythmia. Absolute arhythmia was noticed in 59, or 60 per cent., of the autopsied cases at the Massachusetts General Hospital. A regular pulse was recorded in 39 cases. In the remaining 22 there was no adequate record. In the Boston City Hospital 27 cases, or 56 per cent., showed absolute arhythmia and 21 regular pulses. In the series not autopsied 56, or 53 per cent., showed absolute arhythmia and 50 a regular pulse.

Hoarseness was noticed in three of the autopsied cases at the Massachusetts General Hospital and in one at the Boston City Hospital; also in one of those not autopsied. In two of these cases laryngoscopic examination showed paralysis of the left recurrent laryngeal nerve.

The figures in relation to *precordial pain* are shown in Table XXI. It is notable that this symptom seems to be not at all uncommon in mitral stenosis.

TABLE XXI.—Precordial Pain.

	Present.	Absent.
M. G. H. autopsies	12	14
B. C. H. autopsies	13	4
M. G. H. not autopsied	29	21
	54	39

Dyspnea is perhaps the commonest of all the symptoms in mitral stenosis. Among 130 cases autopsied at the Massachusetts General

Hospital it was present in 88 and definitely noted as absent in only 10; present, that is, at some time during the history of the case. At the Boston City Hospital it was present 47 times, absent but once. In the non-autopsied series dyspnea was present 92 times and absent 8 times. The duration of this symptom in 82 cases autopsied at the Massachusetts General Hospital is shown in Table XXII.

TABLE XXII.—Dyspnea: its Duration.

Less than one week	5
One week to four weeks	15
One month to three months	10
Three months to six months	11
Six months to one year	7
Over one year and less than three years	6
Over three years and less than six years	5
Over six years and less than ten years	6
Ten years and over	10
Indefinite and varied durations, "for years" "some" "since rheumatism" etc.	7
	82

Cough was the symptom next in frequency. In the Massachusetts General Hospital autopsied cases it was present 59 times and absent 8 times. In the Boston City Hospital series it was present 28 times and absent 8 times. In the non-autopsied cases it was present 57 times and absent 29. As regards cough, as with the preceding symptom, dyspnea, the difference between the cases of "pure" and those of "complicated" mitral stenosis was slight.

Cyanosis was present 44 times and absent 28 in the Massachusetts autopsied cases. In the Boston City Hospital autopsies it was present 29 times. No record was kept in 40. In the non-autopsied series it was present 37 times, absent 38. In all three of these series, cyanosis was much more common in the complicated than in the "pure" cases.

Jaundice was present 3 times in the Massachusetts General Hospital autopsied series, twice in the Boston City Hospital series, and 10 times in the series not autopsied. In one of these cases stones were found postmortem in the common duct as an explanation of the jaundice. In the others it was not explained.

Edema of the extremities was present 62 times and absent 27 times in the Massachusetts autopsied series; present 33 times and absent 37 in the City Hospital series; present 47 and absent 65 times

in the series not autopsied. In all three series the cases with more than one valve lesion showed a higher percentage of edema.

Hydrothorax was present 25 times and absent 77 times in the Massachusetts General Hospital autopsies. The other two series were not studied sufficiently minutely, with reference to this point, to make it possible for us to draw any conclusion. The hydrothorax, when present, was unilateral in 15 cases, bilateral in 10 cases.

Ascites was present 27 times and absent 18 times in the Massachusetts General Hospital autopsied series. In the complicated cases ascites was demonstrated in one-third. In the pure cases it was somewhat less common, 18 out of 63, but the difference is not very marked. At the Boston City Hospital ascites was present in half the complicated cases and one-third of the simple cases. In those not autopsied, it was in only 8 out of 116.

The nutrition of patients in all three groups is shown in Table XXIII.

TABLE XXIII.—Nutrition in Mitral Stenosis.

	M. G. H. 111 autopsies.		B. C. H. 67 autopsies.		M. G. H. 115 cases not autopsied.	
	Pure.	Complicated.	Pure.	Complicated.	Pure.	Complicated.
Obese	4	0	6	0	1	1
Good	43	19	21	6	54	9
Fair	8	4	14	3	25	1
Poor	23	3	9	2	12	6
Emaciated	3	4	6	0	5	1
	81	30	56	11	97	18
	111		67		115	

The blood-pressure measurements are shown in Table XXIV.

TABLE XXIV.—Systolic Blood-pressure (M. G. H.).

AUTOPSIED CASES.

80 to 100 in	6 cases.
101 to 120 in	10 "
121 to 140 in	7 "
141 to 160 in	6 "
161 to 180 (cerebral hemorrhage or chronic nephritis) in	4 "
181 to 200 (chronic nephritis) in	2 "
225 (cerebral embolism, aortic stenosis, mitral stenosis) in	1 "
	36

NON-AUTOPSIED CASES.

150 or below in	23 cases.
Above 150 in	8 cases.

The liver was felt in 38 cases, not felt in 51 at the Massachusetts General Hospital in the autopsied series. In the Boston City Hospial series it was felt in 27, not felt in 27. Taking separately the cases of multiple valvular lesions, the liver was felt in 16, including the autopsied series at both hospitals, and not felt in 17. In the non-autopsied series the liver was found in only 13 out of 106 in which it was felt for.

The spleen was enlarged in but 4 of the cases autopsied at the Massachusetts General Hospital and in 4 of those autopsied at the Boston City Hospital. Curiously enough, in those not autopsied the organ was also felt precisely four times.

Delirium was noted in 9 out of 70 cases autopsied at the Boston City Hospital.

MANNER OF DEATH

Death was sudden or unexpected in 21 of the cases autopsied at the Massachusetts General Hospital and in 10 of those autopsied at the Boston City Hospital. In most of these the autopsy showed no explanation of the sudden termination.

I wish to call special attention to the fact that only 20 per cent. of the pure mitral cases and 50 per cent. of those with other valve lesions died of what is ordinarily known as a "cardiac death," *i. e.*, death from asystole. 60 per cent. of the pure mitral cases and 27 per cent. of the complicated died with most of the evidences of acute septicemia, while 16 per cent. of the pure mitral cases and 7 per cent. of those with multiple lesions died from some cause unconnected with the heart. (See Table XXV.)

TABLE XXV.—Mode of Death (M. G. H.). One Hundred and Nineteen Autopsied Cases.

	Acute septic death.	Cardiac death (mechanical).	Death from diseases of other organs.
"Pure mitral" cases . .	53 (60%)	17 (20%)	16 (20%)
Mitral with other lesions .	9 (27+%)	17 (50%)	7 (22%)
Total . . .	62	34	23

SUMMARY AND CONCLUSIONS. One must be prepared to make a diagnosis of mitral stenosis not only in cases in which typical auscultatory signs are present, but also under the following conditions:

1. When in a case with a well-marked rheumatic history extending over many years the signs are those ordinarily associated with mitral regurgitation.

2. In cases presenting the clinical picture of malignant endocarditis, with a history of rheumatism, chorea, or long-standing endocarditis some years earlier.

3. In cases of cerebral or peripheral embolism, especially when they occur in relatively young people who have a clear history of chorea, rheumatism, or endocarditis.

4. Mitral regurgitation rarely if ever causes death. Like ascites or hydrothorax it is a subordinate item, the result of arteriosclerosis, of nephritis, syphilitic aortitis, pneumonia, or some other disease.

5. On the other hand, mitral stenosis, itself the result of previous endocarditis, may be directly a cause of death. It is often independent of any lesion in other valves.

6. If there is associated with mitral stenosis a rheumatic process on the *aortic* valves, the latter is usually much less extensive and less important.

7. Soft, early-diastolic murmurs, loudest along the left sternal margin, are often present in mitral stenosis with sound aortic and pulmonary valves. Such murmurs may be falsely interpreted as due to aortic regurgitation; as a result of this mistake the apical presystolic murmur may also be falsely interpreted as one of the "Austin Flint" type and thus the diseaase at the mitral valve may be missed altogether in diagnosis.

8. In about 20 per cent. of the cases in this series the presence of mitral stenosis was wholly unsuspected until the time of autopsy. In these cases the chief causes of death diagnosed during life and proved at autopsy were such diseases as cirrhosis of the liver, empyema, pneumonia (four cases), gastric ulcer with hemorrhage, tuberculosis of the hip (with osteotomy), ulcerative colitis with perforation and general peritonitis, uterine fibroid, dying of hemorrhage after laparotomy. One case died with the clinical picture of acute lymphoid leukemia, another with a syphilitic stricture of the rectum, and three with cerebral hemorrhage.

9. Sixty per cent. of the cases of pure mitral stenosis in this series died with the clinical picture of an acute infection (acute septic endocarditis) rather than from asystole and mechanical causes.

10. Pure mitral stenosis may be associated with a marked displacement of the apex impulse downward as well as outward, and with a very considerable increase in the weight of the heart.

DISCUSSION

Dr. James B. Herrick: I think the study Dr. Cabot has given to us is of extreme value and of great interest, if for no other reason than that it teaches us humility, and not to be overconfident when we come to the examination of our patients. At the same time I confess there is a little something in it that rubs me the wrong way. According to what he has said, it is possible for us to diagnose only about 50 per cent. of the cases of mitral stenosis. But may there not be certain extenuating circumstances? May we not ask Dr. Cabot if there is not something in the context that he has omitted? We are justified in asking him, whether he or some one equally as competent made the examinations, or were many of them made as they are in many hospitals by young, perhaps inexperienced internes or residents? Who interpreted the results? Then, again, we are justified in asking whether some of these patients—perhaps many of them—were not practically moribund when they entered, when a careful, thorough examination was practically impossible or, if it were made, clearly unsatisfactory? In what percentage of the cases of mitral stenosis had the heart muscle gone to pieces, become thoroughly incompetent, accompanied by the irregularities of auricular fibrillation in which condition a diagnosis is at best often only a tenative one. Again, what percentage of cases had some complication, some disease in organs other than the heart that stood out so prominently that the attention of the physician, the surgeon, or the interne perhaps—was distracted away from the heart, the heart really overlooked, and no examination of it made? That, in a certain sense is not a failure in diagnosis; it is not an inability to interpret cardiac phenomena; it is a blunder; it is a failure to examine. As I have said, there is something in his paper that rubs me the wrong way. When the statement gets into the medical and lay press that only 50 per cent. of these cases were recognized, the impression is conveyed that this represents the ability of the average well-trained physician to diagnose mitral stenosis. I believe the average physician of training, if given a chance to examine the patient before he is virtually moribund, can if he is careful reach correct conclusions in a larger percentage of these cases. And so I must enter a mild protest against Dr. Cabot's way of putting forth these statistics.

Dr. W. S. Thayer: I should like to ask Dr. Cabot two questions: first, in those cases which have come to this clinical and pathological conference,

how does he reach the diagnosis; has he seen the patient himself or does he rely upon the notes of others; and secondly, in those instances which he has not had at the clinical and pathological conference, how does he determine what the clinical diagnosis was in a given case? It is very difficult in most hospitals to determine from the records alone what the diagnosis of the physician in charge of a certain patient was. The visiting physician rarely records his diagnosis at the time of the visit. Furthermore, I have known it to happen in hospitals with which I have been connected that the history has not really been made up and deposited in the record until after the necropsy, so that the recorded diagnosis sets forth not always the opinion of the clinician before necropsy but the nature of the case as determined by the later investigations. It is only in the last few years that we in Baltimore have been in the habit of dictating our opinions as to the nature of the case at the end of each note. Now it seems to me very difficult in many instances to determine what the diagnosis was in the mind of the observer from the records alone, and secondly as a result of considerable personal experience I am sure that the accurate diagnosis of the nature of any cardiac lesion based upon the perusal of the dictated notes of another is a very difficult matter. The accuracy of such diagnosis cannot be compared with the accuracy of the diagnoses of a good clinician in cases which he has observed himself; the final conclusion in many instances of valvular cardiac disease depends upon a number of delicate points which one can only determine for himself.

There are a good many instances in which mitral stenosis passes unnoticed—and these statistics of Dr. Cabot's emphasize this point—but I do not believe that Dr. Cabot would assert—indeed, I am quite sure he would not—that he himself would make so large a proportion of incorrect diagnoses in cases which he had been able to follow himself. Moreover, I shall not hesitate to say that if he does believe this to be the case, I must beg leave to differ with him—I know him too well and have too high a regard for his diagnostic ability. His statistics, however, are as always most interesting and furnish food for thought.

With regard to the diastolic murmur heard along the left sternal margin in so many instances; this brings up a rather interesting question. I wonder how many of these may have been murmurs of relative pulmonary insufficiency. There is never any difficulty in distinguishing a diastolic murmur arising at the aortic or at the pulmonary orifice from a diastolic murmur arising at a mitral valve. Diastolic murmurs of mitral origin always begin at a period, slightly perhaps, but definitely after the sound due to the closure of the aortic and pulmonic valves, and are preceded by and separated from these sounds by a slight pause; this, apart entirely from the character of the murmur and the area in which it is heard. They begin often, to be sure, very early, at the time of the third sound, but they are perfectly distinct in time from the diastolic murmur of aortic insufficiency which replaces or continues the second sound.

In a considerable number of instances of mitral stenosis, however, an early diastolic murmur of pulmonic insufficiency may be detected over the right ventricle along the left sternal margin and in the region of the pulmonic valves, the so-called Graham Steele murmur. I have recognized this in a number of instances in the last several years in patients who have come to necropsy and registered my diagnoses at the clinical and pathological conferences; in all these cases marked dilatation of the right ventricle with dilatation of the pulmonic ring has been observed. It is not uncommon to be able to hear a long diastolic murmur of mitral stenosis over the right ventricle. As one approaches the base it may become so faint and soft as to resemble somewhat an aortic diastolic murmur but by its time of onset it may always be distinguished accurately from the diastolic murmur which accompanies either aortic or pulmonic insufficiency.

Dr. L. F. Barker: Dr. Cabot has not said very much about the changes in the myocardium which are so often found along with valvular lesions of the heart. It is quite possible there was a mitral insufficiency in some of these cases in which the left ventricle was enlarged; or there may have been a complicating myocardial lesion to account for the size of the left ventricle.

Again, as to the murmur at the left sternal margin, I think it is hard to see how the mitral stenosis alone could give rise to that.

Dr. Cabot (closing): All this talk about these diagnostic mistakes being excusable I have heard many times before, and all I can say is that it is not so. If you gentlemen had made the same observations that I have, you would get the same results. I do not flatter myself that my diagnoses are any better than yours. Some of these cases were studied by men as good as I am and better, who found not the slightest trace of trouble during life; yet at autopsy they found mitral stenosis. The findings naturally made a deep impression upon them.

I remember a case of cancer of the pancreas in which the heart was carefully examined, though in a routine way. There was a deep jaundice, and all attention was centred upon the one thing, but we did not neglect the heart, and we missed the lesion. Some of these mistakes are due to the fact that others write the records while I make the diagnosis. I try to make diagnoses as good as I can. Some of the patients were seen when they were in a moribund condition; nevertheless an attempt was made to make a diagnosis. In ordinary practice we have got to try to make a diagnosis of moribund cases. We have got to do something.

Auricular fibrillation was present in 50 per cent. of the cases. That should not prevent me from making a diagnosis.

As to the diastolic murmur, we looked each time postmortem to see whether there was any evidence of such a condition as Dr. Thayer spoke of, *i.e.*, a dilatation, or any evidence of high blood-pressure in the pulmonary artery, but we find that hypothesis does not rest on a firm foundation.

As to the remarks of Dr. Barker concerning myocardial changes, I will

say the pathologist found no myocarditis. He did not cut the heart into blocks the size of a pea and examine every single block as Krehl says we should. With ordinary examination we did not find myocarditis.

I have no doubt there was mitral insufficiency as well as stenosis in these cases.

As to Dr. Barker's point that nobody dies of mitral insufficiency *or of mitral stenosis*, that is true of some cases. Cases said to die of mitral stenosis may die from some other disease or condition outside of the heart, as from pneumonia, from septicemia, from some condition that has no direct connection with the heart. But cases which I said died of mitral stenosis—and there was a considerable number of them—are those in which the cause of death could not be referred to any other organ outside of the heart.

EXPERIMENTAL BACTERIAL INTERSTITIAL NEPHRITIS

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The presence of kidney lesions in individuals suffering acute intoxications and infections, is universally recognized, but the relation of these acute disturbances to subsequent and permanent renal damage still offers great difficulty to the clinician and pathologist. That the kidneys should respond to many varieties of intoxication is obvious, and that the response may, at times, be within the bounds of its physiological activity, at other times overstep this limit and be pathological, is also evident. Where the dividing line between the physiological and the pathological processes falls is hard to indicate, save where we set a normal objective standard for the clinician and pathologist. For the clinician this had been done by Richard Bright (1828). For the pathologist many have been indicated (Rayer, Reinhart, Frerichs, Wilkes, Ribbert, Weigert, and others), and recently Vollhart and Fahr have set forth a new classification, which means to correlate the clinical and pathological findings for a fuller understanding.

A common agreement has been reached in recognizing two distinct types of changes in the diseased kidney, the regressive or degenerative and the progressive or proliferative. Each of these may appear in the absence of the other, but not uncommonly they occur together, appearing either simultaneously or one of them may be primary. Difficult it is, however, to determine what part each of the tissue reactions has played in bringing about the manifestations noted during life, and the relation of the cellular changes to each other needs further investigation. Whether, as Aschoff has

indicated, the inflammatory process is much more comprehensive in kidney diseases than is accepted by most, appears to rest upon the individual views of the inflammatory process. Whether cloudy swelling and its sequel is viewed in the light of inflammation is an issue of significance not isolated to the kidney.

It is of interest to note that not a few of the studies upon true nephritis of one kind or another have been made upon the kidneys of infectious cases in which the heart was concurrently involved. These studies have been particularly interesting in demonstrating a variety of lesions (in all stages of the disease), in which tubular and glomerular degenerations were demonstrated. Moreover, microscopic embolic lesions of the glomeruli have recently received much attention (Gaskell, Baehr). In many of the studies upon human material, individual authors have laid particular stress upon one or another finding as indicating the significant process of the kidney in the disease. When, however, we correlate these pathological observations, a rather complex reaction is found to be present. In other words, so various may be the exciting cause in its effect upon the kidney structure that though a dominant character may be outstanding, a complicated involvement of different structures changes the general appearance. It is also evident that such a sensitive organ as the kidney will respond not only to the initial agent of the disease, but as sytemic derangements occur, will also show the effects of these.

Experimental kidney lesions have been induced by a variety of chemical agents, the salts of mercury, uranium and copper being chiefly studied. Organic compounds (tartrates and acetates), alkaloids (cantharadin, aloin), and venoms have also been found effective in bringing about severe renal disturbances. In the main, these lesions have consisted in degenerative processes affecting the secretory cells, but some have also observed the presence of interstitial inflammatory reactions, as well as vascular and glomerular lesions. The point here to be noted is that many soluble chemical bodies brought to the kidney by the circulation act upon that portion of the kidney structure which deals with them in the process of excretion, and the damage of the renal structure is, for the most

part, observed in the parenchymatous cells as a degeneration, varying from a mild granular and edematous change of the protoplasm to the more serious nuclear disturbances and complete death of the cells. However, alterations are also observed in the interstitial tissues, glomeruli, and bloodvessels, where an edema, proliferation of connective tissues, or a mild inflammation with cellular exudate is not uncommon. We mention these combinations of reactions merely to indicate the complexity of the reactions which also attend the experimental lesions, where a single agent has been used.

The frequency of kidney disease associated with infective heart lesions led us to isolate, from a series of primary or recurrent cardiac disease, the organisms, obtaining them either during life in blood cultures or from the heart blood at autopsy. These organisms all belong to the group of streptococcus viridans (Schotmüller), and by cultural means have been classified by my colleague, Dr. W. L. Holman. From cases of infective endocarditis we have isolated the Streptococcus salivarius, Streptococcus fecalis, Streptococcus mitis, and Streptococcus equinus. These organisms as well as similar ones isolated from different sources (mouth, throat, intestine, feces) were used for the inoculation of animals. For the most part emulsions of a luxuriant growth on blood agar were inoculated into the ear vein of rabbits. Heavy growths in serum broth were also used in a few cases, but were discarded as bacterial clusters and precipitated albumen could not be avoided in the materials for inoculation. All of the cultures were relatively recently isolated, and some were used as soon as they could be grown on media and their purity demonstrated. In no instance did suppuration arise either at the point of inoculation or in the internal organs. In many animals repeated inoculations were made, as it was found that the organisms rapidly disappeared from the blood stream. It was found, however, that although the blood might be free from organisms these could be occasionally demonstrated in the internal tissues (spleen, kidney, liver, and lymph glands). After varying intervals the animals were killed or died. Tissues were then collected at autopsy and fixed in Zenker solution and formalin.

TABLE I

Case.	Number.	Culture.	Type of streptococcus.	Inoculation.	Total interval before death.	Death.
1	XVI	391.0	S. salivarius	June 7, 1913	2 days	Died
2	I	223.0	S. salivarius	Nov. 11, 1912	4 days	Died
3	XXXV	531.6	S. fecalis	Dec. 22, 1913 Dec. 26, 1913 Dec. 30, 1913	9 days	Died
4	XXXIX	520.0	S. salivarius	Dec. 22, 1913 Dec. 26, 1913 Dec. 30, 1913	11 days	Died
5	IX	260.0	S. mitis	May 19, 1913	15 days	Killed
6	X	339.0	S. equinus	May 20, 1913	15 days	Killed
7	XI	312.0	S. mitis	May 20, 1913	16 days	Killed
8	XXXVI	531.6	S. fecalis	Dec. 22, 1913 Dec. 26, 1913 Dec. 30, 1913 Jan. 3, 1914 Jan. 6, 1914	16 days	Died (pneumonia)
9	XXIV	372.2	S. viridans	June 23, 1913	20 days	Died
10	VIII	247.0	S. mitis	Dec. 3, 1912	31 days	Died
11	XXXVII	463.0	S. mitis	Dec. 22, 1913 Dec. 26, 1913 Dec. 30, 1913 Jan. 3, 1914 Jan. 6, 1914	31 days	Killed
12	XII	369.0	S. fecalis	June 4, 1913	33 days	Killed
13	XIII	371.2	S. viridans	June 4, 1913	33 days	Killed
14	XIV	371.4	S. mitis	June 4, 1913	33 days	Killed
15	XXIX	369.1	S. fecalis	Oct. 8, 1913 Oct. 24, 1913 Nov. 17, 1913	41 days	Killed
16	XVIII	212.0	S. fecalis	June 16, 1913	43 days	Killed
17	XIX	391.0	S. salivarius	June 16, 1913	45 days	Killed
18	XV	337.0	S. salivarius	Mar. 19, 1913 Apr. 4, 1913 Apr. 11, 1913 Apr. 24, 1913 May 3, 1913	47 days	Killed
19	XXIII	224.0	S. fecalis	June 24, 1913 Aug. 11, 1913	49 days	Died
20	XXVIII	391.0	S. salivarius	June 25, 1913 Aug. 11, 1913	49 days	Died
21	V	223.0	S. salivarius	Dec. 3, 1912 Jan. 24, 1913	52 days	Killed
22	XVII	260.2	S. fecalis	June 7, 1913	53 days	Killed
23	XXII	334.0	S. salivarius	June 24, 1913 Aug. 11, 1913	53 days	Killed
24	XXVI	369.0	S. fecalis	June 25, 1913 Aug. 3, 1913	53 days	Died (pneumonia)
25	III	223.0	S. salivarius	Nov. 16, 1913 Nov. 25, 1913	83 days	Killed
26	XXI	339.0	S. equinus	June 24, 1913 Sept. 19, 1913	105 days	Killed (cocidiosis)

Case.	Number.	Culture.	Type of streptococcus.	Inoculation.	Total interval before death.	Death.
27	XXV	385.0	S. mitis	June 25, 1913 Sept. 19, 1913	105 days	Killed
28	XX	210.5	S. viridans	June 16, 1913 Sept. 19, 1913	103 days	Killed
29	VII	212.0	S. fecalis	Dec. 3, 1912 Feb. 1, 1913	125 days	Killed
30	VI	224.0	S. fecalis	Dec. 3, 1912 Feb. 1, 1913	134 days	Killed
31	XXVII	210.3	S. viridans	June 25, 1913 Sept. 19, 1913 Oct. 13, 1913	148 days	Killed
32	XL	369.1	S. fecalis	Oct. 8, 1913 Oct. 24, 1913 Nov. 12, 1913	149 days	Died (pneumonia)
33	II	224.0	S. fecalis	Nov. 11, 1912 Nov. 15, 1912 Nov. 25, 1912 Feb. 1, 1913	163 days	Killed
34	IV	212.0	S. fecalis	Nov. 21, 1912 Nov. 25, 1912 Feb. 1. 1913	228 days	Killed
35	XXXV	Control	antihuman red-blood cells, amboceptor, rabbit			
36	XXXVI	Control	Normal (young animal)			
37	XXXVII	Control	Normal (full grown)			
38	XXXVIII	Control	Normal (full grown)			
39	XXXIX	Control	Normal (full grown)			
40	XL	Control	Normal (young animal)			

In all, 40 rabbits were used in the experiments, of which 6 served as controls. Of the remaining 34 which received treatment, 4 were excluded from consideration on account of other spontaneous disease, 3 having pneumonia, and 1 showing a coccidial infection of the liver. Some of the treated animals died shortly after the first or subsequent inoculations. In them the dose of organisms given was too great for the primary resistance of the individual animal. Other animals receiving the same amount of the same organisms withstood the infection without fatal results. A comparison of the tissues from animals dying at different intervals gave a good picture of the character of the reaction in its different stages. It was also noted that some animals receiving a single injection, and

more particularly animals receiving repeated inoculations, became progressively emaciated and died at fairly long intervals after the last treatment. Such a progressive effect upon the animals is suggestive of a latent infection, or it may be of severe damage upon vital organs, which spontaneously become worse. The systemic derangements are not alone referable to the damage upon kidney substance, for in not a few are lesions also demonstrable in the heart muscle, endocardium, and vascular system. Concurrent organic lesions were demonstrated as follows:

Myocardium (either as perivascular infiltration or fibrosis)	14
Valvular endocardium (recent deposits)	5
Pericardium (recent exudate)	2
Arterial (aortic endarteritis)	4
Visceral (perivascular infiltration)	24
Spleen (enlarged)	3
Kidney (interstitial reaction)	24

Our attention was in the main attracted to the lesions of the kidney and reference will only briefly be made of the pathological processes in the other organs. The nature of the processes suggests a classification of the cases into acute, subacute (? recurrent) and chronic nephritis. Sharp lines of distinction do not exist between these groups, but typical examples of each are readily differentiated.

We are not unmindful of the finding of spontaneous lesions in the kidneys of rabbits by Ophuls. He examined 50 rabbits, some old ones, some used for physiological purposes, some previously injected with pneumococci, and others obtained from the market. Of these 50, 10 showed scattered areas of marked interstitial change, with the formation of depressions on the surface, and of these, 4 "proved to be radially arranged chronic septic foci." We have also observed depressions with productive interstitial change in the kidneys of old rabbits, but have missed them entirely in young rabbits (under eight months). For this reason less weight must be placed upon the presence of renal fibrosis in experimental animals which are old at the beginning of the experiment, or which, on account of the duration of the experiment over months of time, advance to an age over twelve or fourteen months. The presence of definite acute kidney lesions early in the experiment, and their absence in the controls of the same age is, to say the least, suggestive of their induced

character. Moreover, the demonstration of the bacteria similar to those used in some of the lesions studied is also very significant. It is furthermore to be observed that the renal lesions of spontaneous character are scattered irregularly through the cortex and usually lie quite widely separated. The depressions are the size of small pinheads and are situated between the borders of two contiguous lobules. We have not observed spontaneous lesions causing a granular roughening of the surface of the individual lobules, though I can well see that such may occur if a susceptible animal be affected by a spontaneous infectious disease of long duration. The experimental lesions may be distinguished from the spontaneous lesions referred to by Ophuls by the more extensive dissemination.

Acute Stage of Experimental Interstitial Nephritis. Lesions in the acute stage were observed in the animals which died or were killed at short intervals after the inoculation. The tissue changes of this group were studied in animals receiving only a single inoculation, and which were permitted to live from two to thirty-three days. Toward the end of this period a considerable change in the picture was to be noted, though the reaction was of the nature of an acute process. The acute lesions were also studied in the cases in which repeated inoculations were made, but in only those in which the time from the first inoculation until death was under thirty-five days was the process a purely acute one.

Macroscopically little could be noted in the rabbit kidneys in the early stages which would give one a clew as to the character of the internal changes. Sometimes a swelling of the cortex and a gray or grayish-pink color of its substance suggested a "cloudy swelling." But the presence and distribution of the inflammatory process could not be recognized in the gross.

The first reaction following the inoculation was observed on the second day in the glomeruli. The capillary coils were intensely congested so that the entire glomerulus appeared enlarged and fitted snugly into its capsule. There was no intracapsular crescentic space. The cells of the glomeruli appeared swollen and some were vacuolated. A few lymphocytes were found in the glomeruli as well as about the afferent arterioles just at their point of entrance

through the capsule. None of the glomeruli showed evidence of thrombosis or embolism and all evidence of severe glomerular degeneration was wanting. The convoluted tubules of the first order stained readily with oesin; the nuclear bodies stained poorly, and the cell protoplasm was granular. The majority of the cells were large and occupied the free space of the tubules. There was no evidence of fat or lipoid material in the cells by the microscope.

Where the time before death was increased, the degenerative changes in the kidney remained about the same, but the cellular reaction became greater. This reaction appeared to be distributed along the course of the vascular tree in the kidney substance. The arterioles of the intermediate zone (between cortex and medulla) showed the presence of an infiltration which was mainly lymphocytic, but which also contained plasma cells and occasional leukocytes. About some vessels the amount of infiltration was quite intense, but the character of the cells remained the same, and in no case was there evidence of destruction of the tissue of the involved area to form abscess. The infiltrating cells lay in the widened interstices of the stroma. The looseness of the stroma suggested an associated edema, but the striking feature was the perivascular distribution of the infiltrating cells. As previously indicated the arterioles of the intermediate zone were surrounded by wandering cells of the lymphocytic type, and from these a cellular reaction could be followed along the vascular branches into the cortex and to a lesser extent into the medulla. Elsewhere again an even more marked infiltration was found about the interlobular arteries, which extending from the medulla through the cortex led to the production of radiating bands of cellular reaction through the kidney substance. These bands of infiltration did not alone involve the cellular tissue about the interlobular arteries, but also spread into the surrounding intertubular stroma, so that the kidney tubules of the various orders lying in the interlobular region were surrounded by a cellular exudate. Fibrin was never noted in this exudate, and it was never observed to have purulent characters. Not only were the tubules surrounded by this infiltration but also the neighboring glomeruli. It is to be noted, however, that this inflammatory process in extending through the stroma remained

isolated to the interstitial tissue and did not pass into the epithelium of the tubules. Only rarely were a few leukocytes found within the tubules. Likewise the infiltration remained for the most part on the outside of the glomerular capsules forming compact masses about them. The glomeruli themselves were the seat of cellular exudate only in proportion to the intensity of the individual attack made upon them. Some glomeruli were almost free from reaction, save a congestion and swelling of the cells as observed in the earlier stage. Others again showed the presence of many lymphocytes lying both between the capillary coils, as well as in the capsular space. In the early stages no proliferative response was noted in the connective tissues of any portion of the kidney.

Between these radiating bands of cellular infiltration the kidney substance was less involved in the process. Degeneration of the epithelial cells of the convoluted tubules was more advanced than was noted in the early stage. The epithelial cells were decidely granular and vacuolated but fat was not present. Some tubules showed erosion of the inner surface of the cells, so that an irregular and ragged lumen was produced. Frequently a granular debris was found within the tubules, but only exceptionally were wandering cells present. Where considerable degeneration with erosion of the epithelial cells had taken place the lumen of the tubules appeared enlarged, in sharp distinction to the compressed tubules in the zone of cellular infiltration and to the appearance of the tubules in the early stage of cloudy swelling. Here and there small islands of cellular infiltration were observed within the less involved portion of the cortex. These islands consisted of lymphocytes and plasma cells aggregated about the afferent arterioles of nearby glomeruli. In serial sections some of these periarterial reactions could be traced to the glomeruli. At times the related glomerulus was also infiltrated by lymphocytes, or showed a reaction of edema and congestion.

The changes noted in the glomeruli during this stage of the inflammatory reaction deserve special comment. Congestion and edema of the glomerulus and a varying amount of swelling of the epithelial cells lining the tufts appear to be the early reactions. I have never noted the obliteration of the circulation in the glomeruli during this stage, in fact, the capillaries appear to be unusually dilated and pres-

sure effects could not be observed about the entrance of the arteriole. Subsequently both degenerative and progressive reactions may be found. Degeneration is mainly seen in the epithelial lining of the glomeruli and their capsules. The cells are no longer seen as slender spindles, but are more oval and bulky. Some are quite granular with poorly staining nuclei, while others have desquamated or have disintegrated, forming a granular debris. In a few instances I have been able to demonstrate small hyaline droplets in the epithelial cells of the glomeruli.

The cellular infiltration varied greatly in different portions of the cortex. This reaction was always lymphocytic and ranged from the presence of a few cells to considerable numbers lying scattered between the glomerular loops. In exactly what position these cells lay, whether free in the spaces between the loops or between the endothelial and epithelial cells could not be determined. Some cells, however, were found in the capsular space. These cells of an inflammatory exudate were not associated with an output of fibrin.

Lastly, in the later stages of the acute process a proliferative reaction was evident in the glomeruli. The capillary coils appeared very cellular. These cells were of spindle character and were disposed parallel to the direction of the capillaries over which they lay. Whether these cells were of an endothelial or epithelial character I am not prepared to say, but their presence was more marked in those glomeruli in which a lymphocytic reaction was less decided. These glomeruli showing proliferation were less congested and even appeared as if the circulation with them had been lost. This, however, was more apparent than real, for degenerative change, which could definitely be indicated as the result of proliferative occlusion of the circulation was not observed in any of them.

Undoubtedly, in the radiating bands of inflammatory reaction, the glomeruli as well as the tubules suffered pressure effects from the surrounding exudate. In many instances the tubules and glomeruli were small and compressed so that the usual spaces and lumina were obliterated, but even in the presence of this massive cellular reaction there was little tendency on the part of the wandering cells to pass through the glomerular capsule or the epithelial lining of the tubules.

True embolic lesions of the glomeruli were encountered in a few instances. In them a partial or complete obliteration of the capillaries of the glomeruli had occurred, and all were involved in a greater or less necrosis of the vascular loops. The glomeruli were represented by a homogeneous mass devoid of cellular elements, except for the presence of a few lymphocytes and occasional leukocytes which entered them from the surrounding tissues. At times these glomeruli were quite pink staining, at others there was a blue periphery. In some cases red blood cells were found in the spaces between the glomeruli and the capsules, but extensive and diffuse hemorrhages in the tissues and tubules were not noted. There was commonly a cellular infiltration about the glomerular capsule, which varied in the relative proportion of lymphocytes and leukocytes present, but in none was there evidence of abscess formation. In one instance the demonstration of Gram positive cocci mostly in pairs, but also in short chains of four and five, was readily made. These cocci were found in the glomerular coil, but their exact position in relation to the capillaries could not be determined. In two of the four instances showing glomerular infarction, the heart valves showed recent vegetations. The other two were free from demonstrable deposit, both in the heart and arteries. It would appear that the materials leading to the occlusion of the glomerular capillaries may develop in the circulatory blood, or that the lodgment of small embolic masses of bacteria within the glomerulus leads to a progressive thrombosis to which the greatest damage is responsible. In our microscopic preparations, although bacteria have been demonstrated in the necrotic glomeruli, we have not been able to determine the exact nature of the plug which occluded the blood current, for with the tissue dissolution of the involved glomeruli, fibrin, emboli, or thrombi might readily suffer such change as to destroy their structure.

The reactions occurring in the arteries, and particularly those of the kidney, are of great importance in analyzing the progressive changes in the kidney at different stages as well as in correlating the experimental findings with those in human renal disease. The arteries are important instruments through which noxious agents act upon the kidney substance, and in some cases (in the human)

appear to be the prime factor in inducing, without other agents, sclerotic processes of the kidney, the primary contracted kidney (Jores). With this latter process, the induction of an arteriosclerotic renal sclerosis, our experiments have nothing in common. The renal arteries of all sizes show no evidence of proliferative or degenerative change which sufficiently alters the size of their lumina to interfere with the nutrition of the essential tissues. True it is in some vessels the endothelial coat appeared to be loosened from the underlying internal elastic lamina and a few cells were found in the new spaces. Some of these cells appeared like wandering cells, others had the characters of fibroblasts.

The arteries, however, appeared of great importance in acting as the means for distributing the essential element which induced the inflammatory reaction in various parts of the kidney substance. Not alone were the bacteria and it may be embolic particles, brought to the glomeruli, but, as we have shown by the remarkable distribution of the inflammatory exudate, the arteries were the important structures around which the reaction was found, and by which the inflammation was led through the cortex. The frequent proximity of the arteries to the veins makes it obvious that the perivascular reaction is also associated with the latter, as was pointed out by Ziegler. The interlobular arteries and the arteries of the intermediate zone always show the greatest perivascular response in all stages of the disease, and from these the afferent arterioles carry a similar, but lesser reaction to and into the glomeruli. The perivascular distribution of the inflammation was striking from the earliest beginning of lesions in our animals. We need not here repeat the details of the inflammatory process, save to remark that the cellular exudate was mainly lymphocytic, in which not a few plasma cells were found. Some leukocytes were present and, after several days, fibroblasts were evident in the neighboring connective tissues. The radiating character of the infiltration was alone due to the normal distribution of the arteries and the perivascular position of the exudate. The distance to which the inflammatory process extended into the neighboring stroma, surrounding tubules, and glomeruli varied in each case.

It is suggested that the perivascular distribution of the inflam-

matory products is dependent upon a richer lymphocytic supply of these tissues; either that the bacteria themselves find a more favorable environment or that their toxic products are collected or eliminated by this route. Upon the solution of this question we can give no evidence. It is, however, to be added that this perivascular position for the inflammatory product is not unique for the kidney structure alone. A similar reaction, though not so constant, was found in the meninges, diaphragm, voluntary muscles, liver, and joints, while with almost equal frequency to that of the kidney was it observed in the heart. The much discussed Aschoff's bodies of the heart, present so generally in acute rheumatic fever, are closely related, if not identical with the perivascular processes in the heart muscle observed in our cases.

A chronological classification of the renal lesions in our animals, as Loehlein made for the human cases of glomerulo-nephritis, was not possible, as the progress of the inflammation and the complementary reactions were by no means constant. Whereas a well marked perivascular inflammatory reaction was still present at the end of four and five weeks in some, others had lost all evidence of the exudate and had been restored to a normal looking structure. Here and there these healed lesions left areas of slight fibrosis, observed particularly in the vicinity of the interlobular arteries, or showed slight pericapsular thickening of the glomeruli. The connective-tissue increase in these tissues was so slight that we were willing to accept these cases as examples of healed nephritis. The amount of permanent damage in them was insufficient to interfere with the function of the kidney.

Subacute Stage of Experimental Interstitial Nephritis. The lesions in the subacute stage are distinguished by the less intense cellular infiltration with evidence of fibroblasts in the involved stroma, as well as by the greater and more diffuse degenerative changes in the epithelium. The character of the cellular elements found in the exudate was similar to those in the acute stage, though the leukocytes were almost wanting and plasma cells were present in greater numbers. The position of the exudate remained perivascular. Commonly focal areas of a more acute character were found in the same kidney in which the subacute

processes were the outstanding features. With all the changes in the perivascular tissues, the arteries showed no sclerotic process in the media or intima which could interfere with the circulation. Fibroblasts and newly developed connective-tissue cells were present in fair numbers in the adventitial stroma, as well as in the supporting framework of the tubules bordering the arteries. Thus the radiating and band-like involvement of the cortex was maintained, and frequently the insertion of these bands into the capsule of the kidney was well marked. Slight depressions on the surface of the organ marked the points where the cortex was involved in proliferative and degenerative change.

The tubular lesions were of two kinds, those in the areas of interstitial involvement and those in the intervening portions where the stroma showed no change. In the former, atrophy and compression of the tubules in the path of the connective-tissue change was well marked. The convoluted tubules of both the first and second order were much shrunken and the lumina narrowed. Fatty changes, in the form of fine granules, were found in the epithelial cells of only a few of these tubules. On the other hand, the tubules in the intervening portions, where the stroma was not involved, showed enlarged lumina, with eroded epithelium and frequently a granular debris on the surface. Fatty changes were not encountered in these structures.

A variety of changes were also present in the glomeruli. Those of a proliferative character were mainly evidenced in a cellular increase of the glomerular loops with occasional connective-tissue thickening of the outer layer of the capsule. Proliferation of the glomerular epithelium, both upon the coils as well as the inner layer of the capsule was not uncommon. A granular debris with exfoliated cells occupied the crescentic space within the glomerular capsule while occasional lymphocytes were still present in the structure.

On the other hand, a degenerative process, the presence of a hyaline band or deposit was quite often observed bordering the capillary loops of the glomeruli. In some glomeruli almost all of the capillaries showed the presence of this deposit while in others it was limited to individual loops. The deposit was of a hyaline type which appeared immediately outside the endothelial coat of

the capillaries. No evidence of a glomerular epithelium could be distinguished upon the coils of the capillaries involved in the degenerative process. The development of this hyaline deposit simulates very closely the process of hyalinization of the glomeruli in the human kidney, as has been described by a number of authors (Vollhart and Fahr). It appeared particularly in the subacute form of a glomerulonephritis or during the stages of repair following an acute lesion.

All degrees of destruction of the glomeruli were evident. Some showed a hyaline process in but a few capillary loops, others had a greater involvement. The presence of blood within the glomeruli varied with the extent of the changes in each coil. Where the hyaline deposit was more advanced, the presence of connective-tissue lamellæ, following the tortuous course of the capillaries, or lying concentrically arranged on the inner surface of the glomerular capsule was always noted. Where the capsule itself showed a fibrous thickening, there were synechiæ which bound the glomerulus to it. These adhesions were most marked at the base of the capsule where the bloodvessels entered it, and from here it advanced until the glomerulus was completely bound. In no instance was a fibrinous exudate found by which a granulation tissue could lead to fibrosis in the stage of repair. It would appear rather that the connective tissue was stimulated to growth mainly through the injury induced upon the glomerular tissues (with its exfoliation of the epithelial lining of the capillaries and capsule) as well as the direct effect of the bacterial irritant upon the interstitial stroma. The complete obliteration of some glomeruli by a hyaline fibrosis was not uncommon. In these, there was no evidence of any patent capillary loops.

Chronic Stage of Experimental Interstitial Nephritis. The chronic stage of the disease was characterized by the development of fibrous tissue in the radiating perivascular bands previously noted, the sclerosing of the involved glomeruli, the atrophy and compression of many tubules of the cortex, and the almost complete absence of wandering cells. Macroscopically the surface of the kidney was puckered and coarsely granular, the depressions being more frequent than the isolated pittings arranged at the points

of intersection of the borders of the lobules. The best results were observed in those animals receiving several inoculations of the same organism at intervals over a fairly long period. Well marked examples were obtained in animals 31 and 33, living 148 and 163 days under observation respectively, while lesser degrees of the chronic stage were noted in animals 28, 29, 30, and 34, surviving from 113 to 228 days after the treatment was started.

It must be remembered that in keeping young animals under treatment for from three to seven months, adds a sufficient time period to their lives to put them in a class in which a certain number of them spontaneously develop some fibrosis in the intermediate zone and along the main interlobular arteries. The more widespread character of the fibrosis, in our experiemnts, following not only the interlobular arteries, but also their branches and advancing to and into the glomeruli, gives, we believe, some distinction for the differentiation of the lesions. Moreover, it was found that when the animals had recently received an inoculation, evidence of a recurrent acute non-suppurative infiltration was at hand in those areas previously discussed.

Where the fibrosis is well developed the tubules are shrunken and small. Some tubules contain hyaline plugs while others show only a slight amount of granular fat. The involved glomeruli are obliterated by a hyaline fibrosis. In the portions of cortex between the masses of connective tissue the tubules appear fairly normal, some are large with dilated lumina. The uninvolved glomeruli are larger than normal, and at times appeared quite cellular. The retraction of the cortex opposite the areas of fibrosis was unusually well shown, and appeared to result as an active process from degeneration and loss of parenchymatous tissue of the part as well as a shrinkage of the connective tissues, rather than from the bulging of the intervening kidney substance in a process of compensatory regeneration. Little evidence of cellular regeneration of the parenchymatous tissues was at hand, save for the enlarged convoluted tubules and some proliferation of the epithelial lining of the enlarged glomeruli.

In general the results of these experiments indicate that a true nephritis may be experimentally induced in rabbits by the inocula-

tion of culture of the different types of organisms belonging to the streptococcus viridans group of bacteria, isolated from man. The response to this infection was the production of a non-suppurative inflammation, lymphocytes and plasma cells being the chief constituent, which was distributed along the renal vessels and their branches. Varying with the intensity of the tissue reaction a variable amount of parenchymatous structure was involved which later suffered from the contraction of the healing stroma, as well as from nutritional change in consequence of glomerular obliteration, as has been pointed out by Loehlein and others. The primary toxic effect of the infection directly upon the parenchymatous tissues was transient and disappeared after the infection had been overcome. The isolation of the inflammatory reaction along portions of the renal arterial system gave an unequal distribution through the kidneys, which subsequently caused an irregular pitting and coarse granulation of its surface. Suppurative processes were never found.

The glomeruli were the seat of both proliferative and degenerative reactions. The former appeared to result from the direct effect of toxic substances arising in the process of infection and was accompanied by a slight lymphocytic infiltration, while the latter was associated with nutritional changes. The production of hyaline fibroid glomeruli was the usual outcome of the involvement of these structures. The embolic occlusion of a part or the whole of the glomeruli was noted in a number of instances, and although not necessarily associated with vegetations upon the heart valves simulated that reported by Gaskell and Baehr in man.

We would draw particular attention to the simultaneous occurrence of glomerular and perivascular lesions in these animals, as a response to a common agent, the streptococcus viridans group of organisms. Much has been discussed in recent literature of the importance of the streptococcus infection in heart disease, scarlet fever, measles, acute rheumatic fever, in inducing a distinct type of Bright's disease distinguishable from others. In these studies attention has been concentrated upon the glomerular lesions, viewing these as the primary and direct cause of the subsequent sequelæ. Thoma, Ziegler, and Vollhart and Fahr take it that the degeneration

of the tubules of the cortex develops in consequence of the nutritional change induced through the obliteration of the glomerular capillaries. The fibrosis about these tubules is viewed as a type of replacement fibrosis which arises passively with the atrophy and disappearance of the parenchyma. Through our experiments, as well as by the examination of human materials, we are led to believe that a perivascular inflammatory reaction is present in the early stages of the glomerular nephritis induced by the streptococcus viridans group, and that a simultaneous proliferative reaction is present in the glomeruli as well as in the stroma of some of the renal arterioles. Furthermore, from our findings, the lesions of the inner coats of the arteries play no important part in the progress of the early or late stages of true interstitial nephritis which, in the end, leads to a type of renal sclerosis. The presence of embolic masses in the glomeruli is only an accident befalling the lesser number of these structures, and causing new complications in an already diseased tissue. Glomeruli in which no embolic process has occurred may suffer a sequence of changes which, in the end, through obliterative hyaline fibrosis, cannot be distinguished from those so affected. The peculiar hyaline degeneration which develops in the subacute stage as a band-like deposit along the borders of the capillary loops of the glomeruli (shown best by the phosphotungstic acid hematoxylin) deserves still greater attention than has been given it, and its elucidation may greatly assist in the explanation of the variable occlusion of greater or less numbers of the capillaries of the glomeruli.

Although the involvement of the glomeruli plays a most important part in the incapacity which the renal parenchyma suffers in this type of kidney disease, the perivascular inflammatory process with the progressive secondary involvement of tubules plays no small part in the final structural change of the organ. The contraction of the kidney substance appears to be a progressive process, resulting from a true inflammatory reaction in the stroma.

Associated inflammatory processes of perivascular arrangement found in the heart, liver, joint capsules, and other tissues suggest a common mode of attack by these streptococci upon many tissues. These findings broadly support the observations of Gull and Sutton,

who, studying the late lesions of nephritis, commented upon the perivascular fibrosis, which was found not only in the kidney but in other organs and tissues of the body.

Moreover, the acute stages of non-suppurative nephritis in man, as have been admirably described and commented upon by Councilman (1897), are capable of reproduction in animals. The importance of glomerulonephritis in scarlet fever, penumonia, and infective endocarditis was at that time pointed out by him. Le Count has recently reported results similar to our own, in which the streptococcus pyogenes of low virulence was used in animal experiments.

The degenerative processes which accompany the inflammatory lesions of the interstitial tissue and the glomeruli consist in the main of a finely granular albuminous precipitate in the protoplasm with the occasional development of a peculiar coarsely granular or globular proteid deposit in the cytoplasm of the convoluted tubules. Fatty degeneration appears to play no important part in the degenerative process. In part at least this parenchymatous degeneration results directly from the effect of the bacterial toxins, as it is observed in the convoluted tubules associated, as well as not associated with glomeruli that have shown circulatory obstruction.

The proliferative changes which occurred in these experimental lesions, leading eventually to a chronic interstitial nephritis or renal sclerosis, have no relation to the fibroses of the kidney which develop secondary to arterial lesions. Jores has fully discussed such processes in man, indicating that an arteriosclerotic process which may effect the renal arterioles as well as those of other organs, and in which the aorta and large arteries may be but slightly involved, leads to a nutritional atrophy of the kidney parenchyma followed by a localized or diffuse fibrosis. Primary arterial lesions were wanting in the kidney of our experimental animals, while the early stages of the renal disease were characterized by the presence of true inflammation. We can, however, well appreciate that in experiments over more protracted periods, and in kidney affections of man, where similar circumstances initiate the process of disease, subsequent arterial affection may induce a vicious circle and lead to changes referable to an obstructed circulation as described by Jores.

What is important to appreciate, is that a form of acute interstitial nephritis induced in animals subsequently gives rise to a renal sclerosis of the type known as chronic interstitial nephritis. We believe, moreover, that a similar process is common in man and that the vascular sclerosis plays a secondary role in bringing about the contracted kidney.

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THE EFFECT OF STRYCHNIN, CAFFEIN, ATROPIN AND CAMPHOR ON THE RESPIRATION AND RESPIRATORY METABOLISM IN NORMAL HUMAN SUBJECTS

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The effects which drugs may, conceivably, have on respiration are of four varieties.

1. They may either stimulate or depress the respiratory centre.

2. They may alter respiration indirectly by increasing or decreasing metabolism.

3. They may alter the general character of breathing, rapid and shallow or slow and deep, or thoracic or abdominal by producing changes in the mechanical conditions within the chest or abdomen, by acting on the circulation, the abdominal viscera or the thoracic or abdominal musculatures.

4. They also may alter respiration by acting as bronchoconstrictors or dilators, and hence altering the dead space in the chest, which necessitates a compensatory change in the ventilation.

The data which must be obtained in studying these various actions are: the carbon dioxid elimination and the oxygen absorption, which give the metabolism; the carbon dioxid tension of the alveolar air and the ventilation of the lungs, which give information as to the excitability of the respiratory centre, and the relation of ventilation to respiration rate, which gives the character of the breathing. In regard to ventilation we wish to emphasize the point, discussed in a previous communication by one of us (D. L. E.[1]), that it is

[1] Edsall, D. L. The Clinical Study of Respiration, Med. Communications, Mass. Med. Soc., 1912, xxiii, 19.

the alveolar and not the total ventilation, which is of importance. The chief function of the respiratory centre is to maintain a ventilation of the lung alveolæ sufficient to keep the tension of carbon dioxid at a definite level. What this level shall be depends on the excitability of the centre. The amount of ventilation necessary to accomplish this result depends on the elimination of carbon dioxid, and hence on the metabolism. Haldane[1] and his co-workers have definitely shown that it is the tension of carbon dioxid in the arterial blood, and hence in the alveolar air (for the tension of gases in the blood leaving the lungs is always practically in equilibrium with that of the alveolar air), which regulates lung ventilation, and that the tension itself will depend on the excitability of the centre. In other words, the ventilation of the lungs will always be such that the carbon dioxid tension of the alveolar air is kept at whatever level the centre requires. This truth having been established, the following relationships will become apparent: First, the elimination of carbon dioxid remaining constant, changes in the alveolar ventilation will indicate changes in the excitability of the centre. Secondly, the excitability of the centre remaining the same, changes in the alveolar ventilation will indicate changes in the carbon dioxid elimination. Also, provided that no acidosis is present—and this assumption is reasonable in the case of normal subjects—or if present, that it remains constant during the period of observation, changes in the carbon dioxid tension of the alveolar air may always be interpreted as indicating a change in the excitability of the respiratory centre.

From the foregoing remarks it will become clear, we hope, that it is the alveolar ventilation and the carbon dioxid tension, rather than the total ventilation and respiration rate, which are of chief importance, in studying the condition of the respiratory centre. We wish to emphasize this point particularly, because in most previous work it has been the total ventilation and rate that have been chiefly studied.

The object of the present research has been, therefore, to investigate the action of the drugs commonly used as respiratory stimu-

[1] The Regulation of Lung Ventilation, Jour. Physiol., 1905, xxxii, 224.

lants, bearing in mind the points brought out above, namely, that the alveolar ventilation and the carbon dioxid tension of the alveolar air are the factors which give information regarding the centre, and that the total ventilation and rate may be subject to wide variation without there being any change in the excitability of the centre, and therefore, that wrong deductions are likely to be drawn when the total ventilation and rate are alone studied. We do not wish to underestimate the importance of observing respiration rate, but we do wish to call attention to the fact that rate has nothing to do, *per se*, with lung ventilation. Ventilation of the alveolæ is carried out entirely, except in such cases of abnormal hyperpnea as that due to pain or emotion, through the chemical stimulation of the respiratory centre by the hormone carbon dioxid. Also it might be well to add here, that it has been recently shown by Hasselbalch[1] and others that this action is due merely to the fact that carbon dioxid (in solution) is an acid; any other acid will also stimulate the centre. In other words, it is apparently the hydrogen ion concentration of the blood reaching the centre that stimulates it. When there is an increase in the production of carbon dioxid, as during muscular work, the carbon dioxid content of the blood reaching the centre will increase, and hence the acidity will increase until the centre by increasing ventilation has restored the alveolar carbon dioxid tension to its former level. This increase in ventilation may be accomplished by an increase in rate, or depth, or both. What determines the method by which ventilation shall be increased, in other words, whether it shall be rate, depth, or both that are increased, is, in all probability, regulated through nervous channels. For instance, the demand for an increased ventilation having been received by the center chemically, the carrying out of this function is probably controlled by afferent nervous impulses. The character of the breathing must accommodate itself to the mechanical condition in the chest and abdomen. Thus in abdominal distention deep breathing may be impossible, and hence a demand for increased ventilation will have to be met by an increase in rate, or, in the case of an em-

[1] Neutralitätsregulation und Reizbarkeit des Atemzentrums in ihren Wirkung auf die Köhlensaurespannung des Blutes, Biochem. Ztschr., 1912, xlvi, 403.

barrassed heart, a sufficient increase in depth may be impossible and an increase in rate must be resorted to.

We are quite ready to admit that observations on total ventilation and rate alone are not without value. For instance, if after giving a drug the rate was found to remain the same and the total ventilation increased, alveolar ventilation must have increased also. If, however, the rate and total ventilation are both increased, the alveolar ventilation might or might not be increased, and the only way to decide the point would be to determine the dead space and calculate the alveolar ventilation. We also wish to emphasize the necessity of studying the metabolism coincidently with alveolar ventilation, for, even though the alveolar ventilation were determined, it would be impossible to tell whether an increase were due to an increased metabolism or to an increased excitability of the centre, unless either the carbon dioxid elimination or the alveolar carbon dioxid tension were determined. It is true that, were an increase in alveolar ventilation found and the carbon dioxid tension unchanged, it might be inferred that the metabolism had been increased. It seems more accurate, however, to determine the metabolism directly as a check on the other findings.

The literature contains a large amount of experimental work on the action of drugs on respiration. This work, with a few exceptions, has been done on animals and by far the greater portion is on the effect of depressants, rather than stimulants. Loewy[1] in 1890 studied the effect of various drugs, chiefly depressants, on the respiration in human subjects. He determined the total ventilation and the increase in it produced by definite increases in the expired carbon dioxid. Camphor is the only one of the drugs that he studied with which we have worked. His results are plotted in the form of curves in which the ordinates are the inspired carbon dioxid percentage and the abscissæ the total ventilation in a given time unit. With two subjects after 0.5 gm. of camphor he obtained in one instance a slight increase (over normal) in total ventilation to a given rise in carbon dioxid tension of the inspired air, but with another subject the results were practically negative.

[1] Zur Kentniss der Erregbarkeit des Athemcentrums, Arch. f. d. ges. Physiol., 1890, xlvii, 601.

In 1892 Wood and Cerna[1] studied the effect of a number of drugs on total ventilation and the respiration rate in dogs. After strychnin there was nearly always an increase in total ventilation. The rate sometimes was increased, and sometimes not. The dosage of strychnin used was from 0.00007 to 0.00019 gm. per kilo body weight, and was sufficient, in most of the experiments, to produce toxic symptoms.

A similar increase in total ventilation, and usually in respiration rate also was noted after atropin. In the case of both these drugs, when both rate and total ventilation were increased, the alveolar ventilation must have increased, but since we do not know the alveolar carbon dioxid there is no means of knowing whether the increase was due to increased metabolism or increased excitability of the respiratory centre.

The same may be said of the work of Impens,[2] who found an increase in total ventilation and rate after the administration of caffein in rabbits. The same author, with camphor and strychnin, obtained negative results.

Biberfield[3] also made some observations on strychnin in rabbits. The respiration rate and total ventilation alone were determined and the results were somewhat variable, in some cases there being an increase in total ventilation, in others not.

Dreser[4] in 1898 carried out some extensive researches on the effect of the various members of the morphin group in rabbits. The animals breathed through Müller valves and the total ventilation was measured with a meter. The oxygen absorption was determined with a modified Regnault apparatus. A decrease in both rate and total ventilation was found with these drugs, most marked in the case of heroin. The alveolar ventilation, therefore, must have been decreased and this presumably was due to a depression of the centre, because the change was very marked, but again we cannot be certain that it may not have been due, in part at least,

[1] The Effect of Drugs and Other Agencies upon the Respiratory Movements, Jour. Physiol., 1892, xiii, 870.

[2] Les analeptiques de la respiration, Arch. de pharmacodynam, 1899, vi, 149.

[3] Zur Wirkungsweise des Strychnins auf das Athmungscentrum, Arch. f. d. ges. Physiol., 1904, ciii, 266.

[4] Ueber die Wirkung einiger Derivate des Morphins auf die Athmung, Arch. f. d. ges. Physiol., 1898, lxxii, 485.

to a decrease in metabolism, for the alveolar carbon dioxid was not determined. The consumption of oxygen after codein and heroin in most of the experiments showed a fall, indicating that metabolism probably did decrease; the carbon dioxid elimination unfortunately was not determined.

Cushny[1] in 1913 studied the effect of caffein and strychnin on the depth and rate of respiration, using a modified body plethysmograph and recording tambour. In the case of both drugs he found the rate increased and the depth slightly decreased. The reaction to carbon dioxid was also tested, and it was found that there was a greater increase in rate after these drugs than before. Here, again, not knowing the alveolar carbon dioxid or alveolar ventilation, we are somewhat at a loss to get the real significance of the results obtained.

The present communication is a preliminary one; it is based on a small number of experiments, but the results seem to be sufficiently striking to make it worth while to report them at the present time.

The methods employed were as follows: The subjects were two normal men, both physicians who voluntarily submitted to the investigation. The experiments were done in the morning, before food was taken (except in the case of Experiment 8, in which a cup of coffee had been taken one hour before experiment was begun) in the recumbent position. The observations on respiration were made with Benedict's so-called Universal Respiration Apparatus.[2] By means of this instrument we measured directly the total ventilation, the carbon dioxid output, the oxygen absorption, and the rate of the respiration. The apparatus was run for ten-minute periods. The subjects were always kept at rest in the recumbent position for half an hour before the first period was begun and did not leave the couch until the end of the experiment. One, or in some cases two, normal periods were run, the drug was then given, and two or three subsequent periods run. The systolic blood-pressure was taken frequently by means of the Faught mercury

[1] On the Pharmacology of the Respiratory Centre, Jour. Pharm. and Exper. Therap., 1913, iv, 363.

[2] Benedict, F. G. Ein Universalrespirationsapparat, Deutsch. Arch. f. klin. Med., 1912, cvii, 156.

apparatus, the figures in the following protocols representing averages or readings just before, just after and during each period. Frequent pulse-counts were made through a long stethoscope strapped to the cardiac area and arranged so that the subject did not know when his pulse was being counted. The figures in the protocols represent averages of three or more counts.

The dead space in the chest was determined for each subject by taking the carbon dioxid tension by the Haldane method and calculating the dead space from this, together with the result of a respiration experiment. This was done from several normal periods on the respiration apparatus and Haldane determinations taken on different days, and the results agreeing satisfactorily, the average was used as the value for the dead space in the calculation. The dead space having been found, the alveolar ventilation was obtained by multiplying the dead space by the respiration rate, and subtracting the product from the total ventilation. The percentage of carbon dioxid in the alveolar air has been calculated with sufficient accuracy for our purposes by dividing the carbon dioxid output per minute by the alveolar ventilation per minute. This has been done for each period and the carbon dioxid percentages given in the protocols were obtained in this manner. The alveolar carbon dioxid has been expressed in percentage rather than as actual tension, because, unless there is a marked change in the barometer, changes in percentage run parallel with those in tensions.

When we began the investigation we believed that the size of the dead space remained constant in any individual. We based this belief on Krogh's[1] recent work in which he found no change in the dead space in a given individual under widely varying conditions, such as extreme muscular work and complete rest. For this reason it did not seem important to make frequent direct determinations of the carbon dioxid tension, and we thought that the calculated values would give us the information we desired. In a second series of experiments now in progress in collaboration with H. L. Higgins of the Carnegie Nutrition Laboratory, however,

[1] The Volume of the Dead Space in Breathing, Jour. Physiol., 1913, xlvii, 30.

we have obtained evidence that some drugs may alter the size of the dead space by acting as bronchoconstrictors or dilators, as mentioned in the beginning of this paper. Of the four drugs discussed here, the effect has been found with atropin only. The question of changes in the dead space will be discussed when we publish this second series, in which a larger number of drugs have been studied and frequent direct determinations of the carbon dioxid tension made.

We have to report eight experiments at the present time, two with strychnin, two with caffein, two with atropin, and two with camphor. One experiment was done with each of the four drugs on each subject. Experiments without drugs have also been done on both subjects, the results of which were perfectly normal. The protocols of the eight drug experiments are given in full.

We wish to thank Drs. O. F. Montgomery and M. N. Smith-Peterson, who not only acted as subjects but also rendered invaluable assistance at the experiments. We also wish to thank Messrs. T. M. Carpenter and H. L. Higgins of the Nutrition Laboratory for much valuable assistance and advice in the use of the respiration apparatus. The experiments in detail were as follows:

REPORT OF EXPERIMENTS

EXPERIMENT 1.—*Strychnin.*—Subject O. F. M. After one normal period and during the first third of the second period, strychnin sulphate, $\frac{1}{75}$ grain, was given subcutaneously. The three subsequent periods show practically no change in the alveolar carbon dioxid tension and a fall in the alveolar ventilation which is strictly parallel with a fall in the carbon dioxid eliminated per minute; a slight rise in the oxygen per minute also occurs. The systolic blood-pressure shows very little change and the pulse a very slight drop; the respiration rate is practically unaltered.

EXPERIMENT 2.—*Strychnin.*—Subject M. N. S-P. In this experiment the dose of strychnin and the method and time of administration were the same as in Experiment 1. We find again a steady fall in the carbon dioxid elimination with a slight rise in the oxygen as in the case of Experiment 1. The alveolar carbon dioxid rises very slightly, and the alveolar ventilation falls somewhat more than in Experiment 1, which is explained by the slight rise in the alveolar carbon dioxid tension. The systolic blood-pressure shows a very slight rise, the pulse a very slight drop, and the respiration rate is unchanged.

EXPERIMENT 1.—SUBJECT O. F. M. EFFECT OF STRYCHNIN[1]

Time.	CO_2 per min., c.c.	O_2 per min., c.c.	R. Q.	Total ventilation per min., liters.	Alveolar ventilation per min., liters	Alveolar CO_2 per cent.	Average respiration rate per min.	Average pulse-rate per min.	Average systolic blood-pressure.
10:44 A.M.	236	279	0.85	6.96	4.67	5.06	12.1	60.0	108
11:17 A.M.	221	299	0.74	7.23	4.37	5.06	15.1	55.5	108
11:40 A.M.	210	292	0.72	6.71	4.16	5.05	13.5	56.0	110
12:12 P.M.	213	291	0.73	7.38	4.26	5.00	16.5	55.5	106
EXPERIMENT 2.—SUBJECT M. N. S-P. EFFECT OF STRYCHNIN[2]									
10:21 A.M.	192	234	0.82	7.07	3.93	4.89	14.5	72.0	108
10:53 A.M.	189	244	0.77	7.00	3.82	4.95	14.7	71.0	108
11:16 A.M.	180	241	0.75	6.86	3.58	5.03	15.2	67.0	111
11:45 A.M.	184	246	0.75	6.98	3.59	5.12	15.7	69.0	112
EXPERIMENT 3.—SUBJECT O. F. M. EFFECT OF CAFFEIN[3]									
11:00 A.M.	219	275	0.80	6.94	4.63	4.74	12.2	55.0	105
11:41 A.M.	245	316	0.77	7.56	4.86	5.04	14.3	51.5	105
12:17 A.M.	230	300	0.77	7.71	4.95	4.64	14.6	51.5	104
12:44 P.M.	224	309	0.72	7.43	4.82	4.65	13.8	49.5	104
EXPERIMENT 4.—SUBJECT M. N. S-P. EFFECT OF CAFFEIN[4]									
10:47 A.M.	180	248	0.73	7.25	3.75	4.80	16.2	72.0	105
11:05 A.M.	192	241	0.80	7.06	3.88	4.95	14.7	72.0	108
11:30 A.M.	201	250	0.80	7.38	4.25	4.72	14.5	66.0	110
11:49 A.M.	205	257	0.80	7.73	4.51	4.54	14.9	65.5	108
EXPERIMENT 5.—SUBJECT O. F. M. EFFECT OF ATROPIN[5]									
8:58 A.M.	226	295	0.77	6.80	4.42	5.11	12.6	59.0	104
9:22 A.M.	221	296	0.75	7.16	4.38	5.05	14.7	57.0	104
10:15 A.M.	253	323	0.78	7.87	5.35	4.73	13.3	78.0	108
10:38 A.M.	258	339	0.76	8.74	5.58	4.62	16.7	80.5	118
EXPERIMENT 6.—SUBJECT M. N. S-P. EFFECT OF ATROPIN.[6]									
2:27 P.M.	171	222	0.77	6.58	3.53	4.85	14.1	66.0	104
2:53 P.M.	178	233	0.77	6.74	3.66	4.87	14.2	67.0	105
3:45 P.M.	194	246	0.79	7.38	4.16	4.65	14.9	82.0	112
4:15 P.M.	186	246	0.76	7.35	4.11	4.52	15.0	87.0	115
EXPERIMENT 7.—SUBJECT O. F. M. EFFECT OF CAMPHOR[7]									
11:01 A.M.	225	285	0.79	6.96	4.48	5.01	13.1	58.0	115
11:28 A.M.	220	278	0.79	7.13	4.09	5.39	16.1	56.0	112
12:09 P.M.	227	304	0.75	6.92	4.35	5.21	13.6	55 0	109
12:34 P.M.	206	277	0.75	6.36	4.04	5.11	12.3	54.5	109
EXPERIMENT 8.—SUBJECT M. N. S-P. EFFECT OF CAMPHOR[8]									
9:37 A.M.	208	240	0.87	7.41	4.08	5.09	15.4	66.5	109
9:56 A.M.	188	239	0.79	7.00	3.74	5.03	15.1	64.0	108
10:50 A.M.	188	237	0.79	7.23	3.90	4.82	15.4	59.0	112
11:35 A.M.	189	238	0.79	7.15	3.95	4.79	14.8	58.0	110

[1] Strychnin sulphate given subcutaneously, $\frac{1}{15}$ grain, during first third of second period.

[2] Strychnin sulphate given subcutaneously, $\frac{1}{15}$ grain, during second minute of second period.

[3] Caffein sodium salicylate given subcutaneously, 5 grains, during first third of second period and 5 grains during first third of third period.

[4] Caffein sodium salicylate given subcutaneously, 3 grains, during first third of second period and 3 grains during first third of third period.

[5] Atropin sulphate given subcutaneously, $\frac{1}{50}$ grain, during first third of second period and $\frac{1}{50}$ grain in middle of third period.

[6] Atropin sulphate given subcutaneously, $\frac{1}{50}$ grain, between second and third periods (3:17 P.M.).

[7] Camphor (in oil) given intramuscularly, 4 grains, during first third of third period and $4\frac{1}{2}$ grains during first third of fourth period.

[8] Camphor (in oil) 4 grains given between second and third periods.

Experiment 3.—*Caffein.*—Subject O. F. M. In this experiment caffein sodium salicylate, 5 grains, was given subcutaneously during the first third of the second period and repeated during the first third of the third period: The metabolism shows a definite rise during the second period, and again falls during the third and fourth. The alveolar carbon dioxid tension shows first a rise, then a fall to slightly below the starting-point. Alveolar ventilation shows some rise. Blood-pressure, pulse and respiration are but little affected.

Experiment 4.—*Caffein.*—Subject M. N. S–P. The results are much more striking. Three grains of caffein sodium salicylate were given during the first third of the second period and repeated during the first third of the third period. The metabolism shows a marked rise, the alveolar carbon dioxid tension a marked drop, and the alveolar ventilation a rise which is proportionately greater than the rise in carbon dioxid per minute. Respiration rate is unchanged. Blood-pressure shows a slight rise and the pulse a slight fall.

Experiment 5.—*Atropin.*—Subject O. F. M. After a normal period, atropin, $\frac{1}{50}$ grain was given during the second period and repeated during the third period. Dilatation of the pupils, dryness of the throat, dizziness and increase in pulse-rate all occurred, showing that we had given sufficient to produce typical atropin action. The experiment shows a marked rise in metabolism in blood-pressure, and in pulse-rate, also a definite fall in alveolar carbon dioxid and a rise in alveolar ventilation which is proportionately greater than the rise in carbon dioxid eliminated per minute. Respiration rate shows a very slight rise.

Experiment 6.—*Atropin.*—Subject M. N. S–P. The results of this experiment confirm those of Experiment 5. Here only $\frac{1}{75}$ grain of atropin was given between the second and third periods. Pulse and blood-pressure show a marked rise; so also does the metabolism. Alveolar carbon dioxid tension shows a definite drop and alveolar ventilation a rise proportionately greater than the rise in carbon dioxid per minute.

Experiment 7.—*Camphor.*—Subject O. F. M. Camphor, 4 grains, given intramuscularly during the third, and $4\frac{1}{2}$ grains during the first third of the fourth period. Metabolism shows a very slight rise followed by a fall. Alveolar carbon dioxid shows a slight rise, and the alveolar ventilation runs parallel with the carbon dioxid elimination per minute. Blood-pressure and respiration rate show a slight fall; pulse remains nearly level.

Experiment 8.—*Camphor.*—M. N. S-P. Here only 4 grains of camphor were given between the second and third period. The metabolism remains

normal, the alveolar carbon dioxid shows a moderate drop and the alveolar ventilation a corresponding rise; blood-pressure a slight rise, pulse a definite fall, respiration rate unchanged.

Discussion of Results. The results obtained with strychnin are clearly negative, except possibly for a slight increase in metabolism. The alveolar carbon dioxid in one instance remained constant, and in the other showed a slight rise. The effect on circulation and respiration rate is essentially negative. It would seem reasonable to conclude that in the case of these two normal individuals strychnin was without recognizable effect on the respiratory centre or the circulation, and also that the general character of respiration is unchanged; it may have slightly increased their metabolism.

Both experiments with caffein show a definite although not very great rise in metabolism. One shows a marked stimulation of the respiratory centre as indicated by a fall in the carbon dioxid tension and a rise in the alveolar ventilation; the other shows the same thing, but to a less marked extent.

The experiments with atropin are in perfect agreement and show a definite rise in metabolism, a marked fall in the alveolar carbon dioxid, and a rise in alveolar ventilation. We thought at first that the latter two effects were due to a stimulation of the respiratory centre, and they probably are in part, but as we mentioned before, subsequent experiments (to be published later) have indicated that this may also, in part, be due to a change in the size of the dead space.

The results obtained with camphor show no constant effects. In one experiment there was a slight fall in carbon dioxid tension, suggesting that there may have been some stimulation of the centre, but in the other experiment there was none. Circulation and respiration rate are essentially unaltered. Metabolism shows a temporary rise in one case, and no effect in the other.

The objection may be raised that these drugs may act differently on sick and on normal individuals. This is highly probable, and we intend to work with pathologic cases later. The effect of the drugs on normal persons, however, should be established first, and the

effect on normal men is of even more importance than that on lower animals, which is what has chiefly been studied.

A single observation has been made with atropin in marked Cheyne-Stokes breathing, occurring in a case of cerebral hemorrhage. Assuming that the Cheyne-Stokes breathing may have been due to a decreased excitability of the respiratory centre, it seemed reasonable to give a drug which we believed stimulated this centre. Enough atropin was given to cause marked increase in pulse-rate; the respiration was recorded by a pneumograph and showed absolutely no change after the administration of atropin. We were unable to obtain the alveolar carbon dioxid tension, as the patient was in coma, and Boothby and Peabody's[1] pharyngeal tube method for obtaining samples of alveolar air had not been published at the time the case was in the hospital.

In this connection the results of Parkinson and Rowlands[2] studying the effect of strychnin in cases of cardiac decompensation are of interest. These authors found no change in respiratory rate after doses of $\frac{1}{15}$ grain of strychnin. They also were unable to observe any alteration in depth, but no means for recording this accurately were employed. In five cases of Cheyne-Stokes breathing absolutely no change in the respiratory curve was found after strychnin.

Conclusions.—We think the following conclusions are justified:

1. Strychnin: No action on the respiratory centre or circulation, possibly an increase in metabolism.

2. Caffein: Stimulation of respiratory centre, moderate increase in metabolism, no effect on circulation.

3. Atropin: Marked increase in metabolism, in doses large enough to cause the classical action on the circulation. Marked drop in the calculated values for alveolar carbon dioxid and rise in alveolar ventilation. Whether these latter effects are due to stimulation of the respiratory centre or to changes in the dead space is not clear at the present writing.

4. Camphor: The results not agreeing, no conclusions are justifiable.

[1] A Comparison of Methods for Obtaining Alveolar Air, The Archives Int. Med., 1914, xiii, 497.

[2] Strychnin in Heart Failure, Quart. Jour. Med., 1913, vii, 42.

INFECTIOUS FORMS OF ACUTE TRANSVERSE MYELITIS

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About two years ago I described an undoubted case of acute transverse myelitis, ending in recovery, and due to the virus of acute poliomyelitis.[1] The patient was a girl aged eighteen years, who developed a complete flaccid paraplegia of the lower extremities, with complete anesthesia in the legs and of the trunk as far up as the lower border of the ribs with an hyperesthetic zone extending to the second rib, in addition to exaggerated deep reflexes and retention of urine. The cerebrospinal fluid revealed a very marked increase of the cells, was sterile, and contained only traces of albumin and of sugar.

In the case of this patient the disease ran such a rapid course that the young woman was discharged from the hospital after seven weeks completely cured.

This case, like several others, occurred at a time when we were still experiencing the effects of a severe epidemic of poliomyelitis, and the neutralization test of the blood of this patient, as determined by Clark in the Rockefeller Institute, gave a positive result. Similar cases have been recorded by Anderson and Frost,[2] by Mosnyes-Moutier,[3] v. Harbitz and Scheel,[4] v. Skoog,[5] and more recently by Netter and Levaditti.[6] In spite of the last named authors, we placed great reliance upon the neutralization test of the blood. It has become somewhat doubtful whether or not this blood test proves the case.

During the past winter in my service in Mount Sinai Hospital we observed a further series of four cases of acute infectious myelitis, three of these patients recovering completely and one dying of the disease. In this last patient the condition was in all probability not due to a poliomyelitic infection. We are therefore compelled to question whether there are not certain forms of acute infectious transverse myelitis which must be distinguished from those due to the poliomyelitic virus. The question also arises whether we are to suppose that cases of acute ascending paralysis, of infectious origin, are in any way identical with acute poliomyelitis. In the three cases ending in recovery the clinical symptoms were uniform. It is necessary, therefore, to give a brief resumé of only two of these.

Case I.—The first case was that of a bright girl (C. S.), aged twenty years, who since her earliest childhood had been a frequent sufferer from tonsillitis. An attack of this sort lasting four days, began on December 8, 1913. The patient noticed during this period a peculiar numb sensation in the legs, a feeling of stiffness, and an inability to void her urine. On the third day there was complete paralysis of the legs and an involuntary movement of the bowels. Twenty-four hours later the arms became paretic. She had no rigors, very slight fever, no vomiting, and no rigidity of the neck. The patient was brought to the hospital on December 18, 1913.

From the records of the case the following may be extracted: Mild horizontal nystagmus; slight left-sided ptosis; hypertrophied tonsils. Heart normal. Complete paralysis of the lower extremities. The knee-jerks, the Achilles tendon reflexes and abdominal reflexes absent. All the deep reflexes of the upper extremities were present. Complete anesthesia from the toes upward to the level of the fifth rib. Complete paralysis of the bladder and of the sphincter ani.

As early as December 20 the knee-jerks were again slightly present, there was slight motility of the muscles of the thighs and the toes could be moved. The hands also show returning power. Two days later there was distinct improvement of motility all over the body, and there was a distinct narrowing of the anesthetic zone.

On December 28 the patient was conscious of the passing of urine. In the course of two weeks the sensory disturbances throughout the entire body had disappeared, the gross power of the legs was again almost normal, and the movement of the bladder and the bowels only slightly interfered with. For a short period of time there was a slight hyperalgesia within the area supplied by the seventh to tenth dorsal segments.

On January 23, 1914, we were able to note that the knee-jerks were lively, that the Babinski and Achilles reflexes could be elicited on both sides. There was complete control over the vesical reflexes. The patient was able to stand and walk with slight support.

On January 31 she was dismissed, completely recovered. It is of interest to add that we concluded to have double tonsillectomy done. Cultures from these tonsils had revealed a presence of staphylococcus albus and streptococcus pyogenes aureus. Blood cultures were negative as was also the Wassermann reaction of the blood and of the cerebrospinal fluid. The cytological examination of the cerebrospinal fluid at the beginning of treatment (at least ten days after the beginning of the disease) showed a normal cell count. The globulin content was not increased.

Case II.—The second case was that of a lady aged thirty years, who had been operated on by Dr. M. for an abdominal tumor. About fourteen days after the operation, in February, 1914, the patient noticed a heaviness of the legs, a numb sensation in the lower extremities, some difficulty in micturition, but at no time were there any rigors or fever.

I had occasion to examine the patient about eight days after the onset of the trouble and noted a marked paresis of the lower extremities, a disappearance of all deep reflexes in the lower extremities, anesthesia to the level of the navel, and retention of urine. According to the statement of the surgeon, the legs had already gained some of their power. There was no evidence of any phlebitis or of any other local disturbance which could possibly have been attributed to the operation. I made the diagnosis of an infectious myelitis of unknown origin and gave a favorable prognosis, basing this upon the evidence that the infection was of a mild order, and largely, also, because other cases of a similar nature, which had been seen at the hospital at this period had taken a favorable course. Within six weeks of this time the patient had completely recovered.

Strangely enough, a young woman who had been a servant in the house of Dr. M., the surgeon who had operated upon the preceding patient was admitted at this time to the hospital, whose illness appeared to be similar to the other two cases described above, but the infection was evidently more severe, and, unfortunately, led to a fatal issue. It is this case which I wish to describe more particularly.

Case III.—M. L., aged twenty-three years, of Irish birth, was admitted to the medical ward of the hospital February 24, 1914. She had always been healthy with the exception of mild attacks of tonsillitis and an attack of malaria two years ago. On February 19 she was taken ill with a cough and hoarseness. Two days later she complained of general malaise, slight chills, but little fever. On the day of admission she had vomited about a tablespoonful of dark blood. She had always complained of chronic constipation.

Careful general medical examination was negative. The only findings

were an increase of the white blood cells and an occasional hyaline and granular cast in the urine.

On the seventh day (March 3) the patient complained of a numb sensation in the right leg which disappeared after a few hours. Two days later she complained of stiffness of the arms and legs; could not sit up in bed. There was no rigidity of the neck, no headache, no vomiting and no Kernig symptom. On March 7 while she was still on the general medical service, it was noted that the patient could only talk in whispers and that there were occasional distinct attacks of apnea. The lower extremities were almost totally paralyzed and there was considerable weakness of the upper extremities. While in this condition she was transferred to the neurological service.

At this time it was noted that the patient presented a marked paraplegia of the upper and lower extremities, being able to move only slightly the toes and fingers. There was no total anesthesia in the extremities, but all forms of sensation were distinctly diminished from the toes upward to the clavicle. Consciousness was undisturbed, so that the patient was fully aware of the tests that were being made. There was distinct atrophy of the inner muscles of the thigh; paralysis of the palate; congestion of the right conjunctiva. All the deep reflexes were abolished as well as the abdominal reflexes. Deglutition was so disturbed that the patient could only be fed with the greatest difficulty. There was distinct dyspnea with occasional short attacks of apnea. The head could be moved easily at all times. There was no rigidity of the neck. The tongue deviated slightly to the right.

On March 11, after taking into consideration the entire development of the symptoms and the course of the disease, we made the diagnosis of a severe ascending paralysis of infectious origin. On account of the imminent danger of asphyxia and the very distressing condition of the patient, I was not willing to risk lumbar puncture. Any attempt to move the patient might have been followed by instant death. These symptoms, including complete paraplegia of the extremities, complete anesthesia from the toes to the clavicle, dyspnea, dysarthria, and incontinence of urine, lasted for about one week longer, the temperature ranging between 100° and 103° F. In spite of the most careful nursing the patient died on March 18, about fifteen days after the onset of the first spinal symptoms.

There can be no doubt that the condition was one of a rapidly ascending paralysis. I suspected a possible poliomyelitic infection giving rise to a Landry form of paralysis. It was evident that the disease in this patient was similar to the mild forms of paralysis which had been observed about this period, and yet I doubt whether

this special form of infectious myelitis could properly be put into the category of a poliomyelitic infection. I requested the Pathological Department and my associate, Doctor Strauss, in particular, to make every effort to get satisfactory evidence on this point. Unfortunately, we were only permitted to do an autopsy of the brain, and inasmuch as there were from the very beginning difficulties of respiration and of deglutition, we were in hopes that some evidence could be gathered regarding the nature of the entire morbid process.

The pathological report was as follows:

The autopsy was done three hours after death. The brain was the only part which we were permitted to examine. The attempt was made to remove it in sterile fashion, but in this we were not successful. Inoculation of a rhesus monkey (intracerebrally and intraperitoneally) developed meningitis and peritonitis within forty-eight hours. Cultures from the exudate revealed streptococci. Inoculation of another rhesus monkey with a 50 per cent. emulsion of the medulla oblongata, the cerebellum and the cortex cerebri yielded a negative result. A second inoculation on the same monkey with the same emulsion was also negative. Anaërobic cultures of the tissues preserved in glycerine, according to the method of Noguchi, were also negative.

A careful histological examination of the medulla oblongata and of the remaining portions of the brain were made. In no part of the brain, and most positively not in the medulla oblongata, was there any perivascular infiltration such as we would have every right to expect in a case of poliomyelitis with cerebral symptoms. Moreover, we found the pia mater absolutely normal. In various parts of the cortex cerebri were noticed a number of small hemorrhages. The ganglion cells of the cortex, of the pons, and of the medulla oblongata were normal. Marchi's stain showed a degeneration of the white fibers in the medulla oblongata. A similar degeneration was found in the fibers of the one plexus brachialis which had been removed postmortem.

However imperfect this autopsy report may appear to be, we may infer with considerable certainty that this patient was not suffering from a poliomyelitic infection. It is all the more regretable that we have not succeeded in determining the special infectious or toxic agent responsible for this fatal myelitis. It is some satisfaction to know that Flexner is of the belief that negative histologic

findings appear to him to yield the most convincing evidence against the poliomyelitic nature of an infectious process. On the other hand, I am inclined to agree with him that it is rather surprising that these various forms of infectious transverse myelitis were observed so rarely in former days and have only become more frequent either during or immediately following upon an epidemic of poliomyelitis. I am also inclined not to change my opinion regarding the poliomyelitic origin of various cases which I have referred to and have recorded in previous writings. It is well, however, to insist that the analysis of the third case recorded in this paper seems to prove that the virus of poliomyelitis is not the only poison which may cause an acute transverse myelitis. It seems also rather premature to consider every case of acute ascending paralysis a form of acute poliomyelitis.

The change that has come over neurological methods of investigation is well illustrated by the fact that the decision as to the poliomyelitic or other infectious character of the disease is to be determined not merely through the histological findings, but that much consideration must be given to inoculation experiments on animals and to the neutralization test of the blood.

Finally, it is well to call special attention to the etiological significance of antecedent tonsillitis in various infections of the central nervous system.

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DISCUSSION

Dr. Simon Flexner: I should like to speak briefly on the points raised in Dr. Sachs' paper. He refers to a case in which a neutralization test was made at The Rockefeller Institute. Unfortunately, I do not remember the precise incidents connected with the case, but there is a larger question involved, namely, what the criteria are that serve to distinguish poliomyelitis from other affections of the central nervous system attended by paralysis. In my opinion there is no test that is conclusive, pathologically speaking, except the history of sections prepared from the central nervous tissues. Absolute reliance cannot be placed upon inoculation experiments, since there are cases of undoubted poliomyelitis in which the nervous tissues fail to communicate experimental poliomyelitis to the monkey upon inoculation. The variations in this respect have ranged from 40 to 100 per cent. positive results. A test which is valuable during life is the study of the cerebrospinal fluid. Hence it would be desirable to know whether in Dr. Sachs' case lumbar puncture was performed and what the fluid yielded. We now know pretty well what the variations of the fluid are in epidemic poliomyelitis. If the changes in the fluid in this case were dissimilar they would tend to exclude it from being an instance of poliomyelitis. No reliance can be placed at present on the efforts at cultivation of the minute organism obtained from cases of poliomyelitis because the method of cultivation is still too difficult and uncertain. The neutralization test is, among the purely laboratory methods capable of being carried out on living persons, one of the very best. It does not give an unequivocal answer for the reason that cases of unquestionable poliomyelitis may fail to bind the virus, probably because the blood is not taken at the best time; and in rare instances normal blood seems to have neutralized the virus. In this connection it is interesting to recall that the blood of persons—nurses and physicians—who have been in attendance on many cases of epidemic poliomyelitis has given a higher percentage of neutralizations than the blood taken promiscuously. Whether this means that persons so exposed undergo an imperceptible immunization to the virus of poliomyelitis can only be conjectured. Furthermore, the fact of recovery from the paralysis proves little as regards the nature of the paralysis since not a few cases of undoubted poliomyelitis, even of considerable severity, recover completely. I consider that what is important in this connection is this: that if there is now occurring with some frequency a form of myelitis previously unknown, or at least unrecognized, in this country, which has begun to appear since the epidemic wave of poliomyelitis, the fact itself is suspicious. If such cases had not been previously observed and yet are so pronounced that they could not very well have been missed, we should consider whether or not, after all, they

are not merely atypical examples of poliomyelitis. On the other hand, if the histological study of the sections prepared from the nervous tissues excludes poliomyelitis I should then be inclined to consider that the case reported by Dr. Sachs belonged to another category.

Dr. Sachs (closing): I have a perfectly open mind as to the identity of these various forms. I am very glad Dr. Flexner attaches so much importance to the microscopic changes, and those after all are the tests.

There is one point which struck me in the clinical course of this condition as being rather different from the fatal cases of poliomyelitis, and that is, those cases of poliomyelitis that terminate fatally usually do so within a few days after the onset of the disease, so that the infection seems to be an intense one, whereas in such cases as I have reported today the disease ran for a period of four weeks; there is a difference probably in the intensity of the action of the virus. Some of these cases recover. Cases of transverse myelitis have been extremely rare, but they were known to occur. Take the case of acute transverse myelitis so clearly described by Professor Kussmaul in his autobiography. The nature of the cause we do not know, but these cases are extremely rare.

We should go on and study this subject, and I hope those who see these cases will take every means of helping us to try and find out the nature of them.

ON ABNORMALITIES OF THE ENDOCRINE FUNCTIONS OF THE GONADS IN THE MALE

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Among the many new facts which have accumulated since the attention of clinicians has been especially directed toward the functions of the glands of internal secretion, none is more worthy of consideration, perhaps, than the evidence first convincingly presented by Bouin and Ancel (1903–1910) pointing to an endocrine function exercised by the interstitial cells of Leydig in the testicles, of fundamental significance for the morphological characters and biological phenomena of the male organism.

Through a long series of investigations (histological, embryological, comparative anatomical, clinical-pathological, and experimental physiological), well summarized in Biedl's treatise[1] and in the monograph of Tandler and Grosz,[2] we now appear to be justified in thinking of the male sex-glands or gonads as divisible into at least two parts (1) a generative part proper, producing the sperm-cells, and (2) an internal secretory part (the interstitial cells of Leydig), producing the hormones upon which depend (*a*) the development of the genital tract in the embryo; (*b*) the development of what John Hunter designated the "secondary sexual properties" of the male, namely, changes characteristic of the male, but "which take place only in parts that are neither essential to life nor generation, and which do not take place till toward the age of maturity," and, perhaps, (*c*) in part, the neural states associated with libido sexualis and potentia cœundi.

[1] Biedl (A), Innere Sekreton, II Aufl., 1913, Bd. ii, 199–343.

[2] Tandler, J. u. S. Grosz, Die biologische Grundlagen der sekundären Geschlechtscharaktere, Berl., 1913, 1–169.

Time will not permit at this meeting of a full analysis of the evidence for this view, but the most convincing arguments in favor of it are based on:

1. The histological resemblance of the Leydig cells (though mesodermal in origin) to the cells of a secreting gland (*Regaud* and *Policard, Loisel, Bouin* and *Ancel*).

2. The observation that in man and in animals cryptorchid testicles are not only dystopic, but smaller than normal, the small size being due to faulty development of the seminiferous tubules, rather than to absence of the interstitial cells of Leydig. Bilateral cryptorchidism is associated with sterility, but not necessarily with loss of male sexual characters, nor with loss of libido. The masculinity of cryptorchids is in direct proportion to the amount of interstitial gland present and independent of the state of the germinative part. In unilateral cryptorchidism, the individual is not sterile, but if the healthy testicle be removed he becomes so, though the masculine appearance and libido are retained as long as the cryptorchid testicle is not removed; if the latter be taken out also, libido disappears and the "masculinity" of the individual definitely recedes.[1] In a few cryptorchids, the interstitial gland is not well developed and hypogenitalism exists; the individuals then resemble eunuchs and are known as "eunuchoids" (*Griffith, Duckworth*).

3. The observations on human males castrated in early life (eunuchs), especially those of Pelikan and of Tandler and Grosz upon the religious sect known as the Skopsi, who practice the horrible rite of self-mutilation. These observations showed the relations of the gonads (as a whole) to the rest of the body. Eunuchs owing to the lack of the internal secretion of the gonads (agenitalism) grow fat, and the fat exhibits a peculiar regional disposition; the larynx and pelvis remain infantile; there is faulty development of the beard; the extremities grow longer than normal; the muscles are hypotonic; the masculine attributes of the psyche are absent—eunuchs are mentally torpid, lack initiative and aggressiveness; they move more slowly and more clumsily than normal males.

[1] Veterinarians have made a careful study of these conditions in stallions; the experiments on the animal described by Whitehead (1908) are especially illuminating.

4. The observations on experimental animals in which:

(*a*) The vasa deferentia are ligatured (histologically and symptomatically reproducing conditions like those met with in cryptorchism).

(*b*) The spermatic cords are ligatured as a whole on each side, symptomatically reproducing conditions like those met with in total castration.

(*c*) The spermatogenic tissue is electively destroyed by exposure to the *x*-rays, while the interstitial cells of Leydig are uninjured. (Genital organs remain otherwise intact; sexual impulse persists; secondary sexual characters remain unchanged.)

(*d*) Castration is done in different animals at different ages (*Steinach, Foá, Nussbaum, Sellheim, Rörig*) combined, sometimes, with transplantation experiments.

5. The observations on animals which exhibit outspoken rutting periods. The behavior of the testicle of the mole (*Talpa europea*) is especially striking; the germinative part is best developed at the rutting period at which time (March) the interstitial gland is smallest; subsequently, the generative part diminishes in size and the interstitial gland hypertrophies to a maximum in July, August, and September. A month or two before rutting the generative part has again become markedly developed, and the interstitial gland has begun distinctly to diminish in size. Thus it would appear that the great development of the interstitial gland is a necessary preparation for the coming spermatogenesis (*Regaud, Lécaillen, Tandler and Grosz*).

6. The observations on premature sex-development in animals and in man. This is physiological in certain varieties of animals known to breeders; in such races of animals, besides the early sexual maturity, there are a number of associated morphological changes (early closure of epiphyses; short extremities with long trunk; early and complete development of external genitalia).

Pathologically early sexual maturity (*pubertas præcox*) has been repeatedly met with in human beings, both male and female (*Haller, Kussmaul, Neurath*). Girls have been known to menstruate in the first year of life, boys to have seminal emissions in the second year of life. Along with these signs of puberty, the

external genitalia enlarge, the axillary hair (*hirci*) and the hair on the mons veneris (*crines pubis*) appeared, the breasts enlarged (in girls) and the voice and psyche changed (in boys). The whole body matured early, but owing to the early closure of the epiphyses (*x*-ray) the individuals had relatively short extremities in proportion to the trunk. It is probable that in such cases a hyperactivity of the internal secretion of the gonads—a so-called "hypergenitalismus"—existed, though this in turn seems to have been stimulated by pathological changes in other endocrine glands (tumors of the epiphysis cerebri; tumors of the inter-renal system or cortex of the adrenal gland).

During the past winter I have had the opportunity of studying a number of patients in whom symptoms existed suggestive of disturbances of the function of the gonads. From the records of these I am selecting two examples: one of them is a eunuchoid with loss of both the germinative and the internal secretory function (hypogenitalism); the other is a dwarf manifesting partial cryptorchidism with loss of the germinative function and increase of the endocrine function of the gonads (hypergenitalism).

Case I.—*Eunuchoid, showing signs of hypogenitalism and of dyshypophysism.*

William Z., white, male, aged forty-three years, boiler-maker. Admitted February 7, 1914.

Complaint. General weakness.

Family history. Father died at eighty-six; was 5 feet 10 inches tall, weighed 250 pounds. Mother died at sixty-five, cancer; medium height; never very stout. One brother, forty-four, unmarried; tall and slim. One brother, thirty-five, married; normal; two children. One brother dead, accident; had one child. One brother died at twelve; born an idiot; had a long head which came to a point in the mid-line; had epileptic fits from birth to death; probably hydrocephalic. No history of tuberculosis in family. Father drank moderately of beer and wine, and smoked heavily.

Past history. In childhood had smallpox, followed by "weakness of the eyes." Scurvy at eighteen, when at sea. Typhoid fever at twenty-two. Lobar pneumonia on the left side at twenty-eight. Chills and fever, probably malaria, eight years ago. Seven years ago he had a compound fracture of the left tibia, followed by osteomyelitis, necessitating an operation. One year ago he had another operation for osteomyelitis of the right leg, six months after having been struck on the leg by a heavy wire cable. During the Boer War he was shot in the right leg.

For the past two or three years he has been subject to rather severe frontal and occipital headaches. His eyes have been "weak" since childhood. For several years he has had a chronic infection of the right middle ear, with almost total deafness on this side, and occasional purulent discharge. A polyp was removed from the nose eight years ago. He has had occasional attacks of sore throat. He states that he has had "fainting" and "giddy spells" for the past fifteen or twenty years. Nocturnal epistaxis occurred regularly every six months after the age of twenty-six. During late years these attacks have occurred every three months.

For several years he has had a cough shortly after eating, and this has often been followed by vomiting, a condition which he thinks is due to smoking. Along with this, his fainting spells have become more frequent.

Three years ago the patient had a sudden, stabbing pain in the left lumbar region lasting one-half hour. One week later he had a similar attack. These paroxysms were associated with some chills and fever, but not with hematuria.

For three years, between the ages of twenty-three and twenty-six, the patient, at regular intervals of six weeks, had hematuria. This flow of blood was painless and lasted about six days. During these six days there was always coincident painful enlargement of the breasts, which was absent during the intervals between the periods of hematuria. After twenty-six the hematuria stopped and the patient had nocturnal epistaxis, occurring regularly every six months. During recent years the nocturnal epistaxis has occurred every three months.

He has never had sexual libido or potentia. He attempted sexual intercourse several times, after the age of nineteen, but the attempts were ineffectual because of inability to obtain an erection.

When cold he has occasional shooting pains in his right thigh, and the leg becomes numb for several days.

The patient is tall and reached his present height at the age of sixteen. In response to criticism by his companions of his feminine characteristics, he has made, he states, many efforts to do "manly work." He has always done hard, muscular work, has been a cow-boy, a soldier in the Boer War, and a boiler-maker.

He is a moderate smoker of tobacco and drinks a small amount of beer.

Present Illness. The onset of the present conditions of weakness was insidious, beginning in 1911. He began to be generally weaker, fatiguing very easily. Recently he has gained fifteen pounds in weight, and has become "flabby" in his muscles.

During the past two years his head and feet have grown larger. His memory and his ability to calculate have become poor, and his visual acuity has, he thinks, been progressively lessening.

Physical Examination. The patient is a tall, round-shouldered, slightly kyphotic, rather obese man of forty-three, with rather long extremities.

Height, 175½ cm. Weight, 190 pounds (calculated normal weight 168 pounds). His skin is smooth and satiny. There is a "freckle-like" pigmentation over the shoulders and arms.

The *facies* and general attitude of the upper part of the body are typical of hyperpituitarism. We note especially (1) the hexagonal shape of the head; (2) the prominence of the lower jaw and chin; (3) the lower teeth over-ride the upper set of teeth—there is prognathism of the lower jaw; (4) wide space between the upper incisors—"hag-teeth"—due to the enlargement of the upper jaw; (5) prominent acra of the face, nose, ears, lips, malar bones, and eye-brows; (6) the hair grows low on the forehead; (7) the skin of the forehead is thick and wrinkled; (8) the characteristic position of the head in relation to the trunk—the head, on a thick neck, sinks down between the shoulders; (9) in the occipital region there is a transverse groove in the skull, and just beneath the groove, an enlarged occipital tubercle.

Hair. The hair on the body and in the face is scanty (for the patient has never shaved). The crines pubis are scanty, and the upper limit of the pubescence is transverse. The axillary hairs (hirci) are scanty, and the beard and moustache are almost absent.

There is a large amount of subcutaneous fat in general, and the fat over the symphysis pubis is abnormally abundant.

The excess of breast tissue is striking (gynecomastia). The pelvis is broad, the thighs curving.

The arms are long, the hands and feet large; the fingers are not definitely spade-like.

The *penis* is short. The testes are rudimentary, being about as large as a lima bean. The prostate is very small, and on massage of the prostate, numerous lecithin cells were obtained, but no spermatozoa. A few epithelial cells were obtained, but no pus.

Thyroid. There is no palpable thyroid tissue; the thyroid gland must be small.

Thorax. Percussion note slightly impaired over the manubrium. Expiration is prolonged, and there are transient fine moist crackles at the right apex posteriorly.

Bradycardia and slight *hypothermia* have been noticeable in the hospital; pulse 56 to 92; temperature, 97° to 98.6°.

The patient has extreme myopia. Pterygium in the right eye. He has some pyorrhea alveolaris, with some dental caries. There is some nasal obstruction on the right side. There is also slight mastoid tenderness and total deafness on the right.

The right great toe has been amputated. Scars of the old operations are visible over the tibiæ.

The patient's memory is poor, and his power of calculation is defective.

Blood Examination. Red blood cells, 5,020,000; white blood cells, 8800; hemoglobin, 80 per cent. (Sahli).

Blood-pressure. 90 to 100 mm. Hg. (Tycos).

Urine. No polyuria. Chemical and microscopic examination negative.

Tuberculin Test (Calmette). 1 per cent.; positive.

Wassermann Reaction (blood). Positive.

Carbohydrate Tolerance. No reducing body was excreted in the urine after the administration of 200 grams of glucose.

Eyes and Eye-grounds. Extreme myopia. Fundic reflex lighter than normal. Optic papillæ oblique. Myopic conus. Both sets of vessels distended. Very slight veiling of the margins of the right disk. Low grade of myopic choroidoretinitis.

Visual Fields. Slight general contraction. No hemianopsia.

X-ray of Head. Normal sella turcica, save for erosion of the posterior clinoid process.

X-ray of Hands. Negative.

X-ray of Feet. Amputation of right great toe. Exostosis on the right astragalus.

X-ray of Thorax. Diffuse infiltration of both lungs (possibly old tuberculous lesions).

Pharmacodynamic Tests. After atropin, gr. $\frac{1}{100}$, the pulse rose from 56 to 64. After adrenalin (15 minims of a 1 to 1000 solution hypodermically) a slight chill, and a rise in blood-pressure from 98 to 118 mm. Hg. (Tycos). No reaction noted after pilocarpin, gr. $\frac{1}{8}$.

This patient's condition at once suggests a multiple endocrinopathy. He presents a combination of symptoms, some of which denote over-action, some, on the other hand, under-action of the hypophysis; the size of the testicles calls attention at once to the defective gonads; the azoöspermia indicates a loss of function of the germinative part and the eunuchoidism suggests loss of the internal secretion of the interstitial cells.

In connection with the hypogenitalism it is interesting to note (1) the account of the patient's occupations. He has always striven to overcome the criticism directed against his feminine characteristics by attempting hypermasculine accomplishments. He has been a cow-boy, a sailor, a soldier in war, and a boiler-maker; (2) the periods of hematuria, along with which there was some swelling of the breasts. This is interesting, and makes us ask whether or not the condition could have been an instance of "male menstruation." The nocturnal, periodic epistaxis also suggests an analogy to the vicarious menstruation of the female.

The hips are broad. The crines pubis are transverse, and there is a moderate accumulation of fat on the abdomen. The thighs are of the feminine type, and there is a tendency to genu valgum, which is common in women. The breasts are larger than normal in the male. He is therefore of the *typus femininus*.

In connection with the dyspituitarism, a possible hypophyseal lesion has to be considered, and a tumor in the region of the sella turcica has been thought of. Of the symptoms which could possibly point to intracranial growth may be mentioned, headaches and slight dizziness, but there has been no projectile vomiting, no choked disk, and no epileptiform seizures. There is also a singular absence of neighborhood symptoms, unless the hypothermia and bradycardia may be so interpreted; there is no hemianopsia and no eye-muscle paralysis, no olfactory disturbance, and no diabetes insipidus. The radiographic formula of the base of the skull, so typical in acromegaly, is not present here. The only *x*-ray anomaly is a flattening of the posterior clinoid process. The symptoms referable to hypopituitarism in the case before us are perhaps just as striking as those of hyperpituitarism, a combination which, as Cushing and others have pointed out, is by no means uncommon. Among such symptoms may be mentioned, the obesity, the genital hypoplasia, and the increased carbohydrate tolerance.

We must conclude that in this case there has been a loss of both the germinative and the internal secretory functions of the gonads (hypogenitalism), together with a dyshypophysism (mixed signs of hyper- and hypopituitarism).

As has been stated the patient has a positive Wassermann reaction in his blood-serum. How the luetic infection occurred we do not know. Coitus has not been possible, but it is conceivable that in attempts at coitus some trauma has occurred which resulted in infection, or extragenital infection may have existed. The patient denies, however, any memory of symptoms or signs suggestive of a primary sore or of secondary lesions. One must think also of the possibility of a congenital lues, especially as profound endocrinopathies have been known to be associated in some instances with congenital luetic infection.

CASE II.—*Dwarfism; unilateral cryptorchism; azoöspermia; hypergenitalism; tuberculous polyserositis; general miliary tuberculosis.*

Robert J., aged twenty-six, colored, laborer, single; admitted to Ward M of the Johns Hopkins Hospital on December 22, 1913 (No. 35,875), under the care of my colleague, Prof. W. S. Thayer, complaining of "pain in the chest, water on the chest, and shortness of breath."

Family History. Father died of tuberculosis; otherwise negative. Both his parents were "large" people. An older brother is "more developed" than the patient. He had four sisters of normal size.

Past History. Aside from measles in childhood and a mild polyarthritis with night sweats two years ago, the patient says he has had no diseases before the present illness. Denies venereal infections. Habits temperate; alcohol and tobacco used in strict moderation.

Present Illness. Onset gradual two weeks before admission with symptoms of a cold (cough and slight expectoration), and pain in the left side and about the heart. He consulted Dr. Hocking of Govans, Md., who found a pleural effusion and sent him to the Phipps Tuberculosis Dispensary for treatment. He was examined in the Dispensary by Dr. Louis Hamman and was sent by him into the stationary clinic.

During his stay in the hospital he was examined by several members of the staff, and on January 9, 1914, I went over him carefully myself. Our records of the case may be summarized as follows:

Colored man; very small stature; height, 151 cm.; upper length, 62 cm.; lower length, 89 cm.; stretch, 151 cm.; fairly nourished but not obese; microcephaly; though small, the head looks mature. Forehead and supra-orbital ridges prominent; nose large; lips not thick; malar bones and zygomata rather strikingly prominent; ears small. Hair high on forehead and recedes at temples; hair on scalp thick; unusually well-developed beard and moustache for a colored man. Hirci abundant; crines pubis abundant but limited by horizontal line above; perineal hair abundant.

Voice high and infantile. Teeth never developed properly; marked heterodontia; teeth not high above the gums; one peg-tooth near mid line in upper jaw; the two medial incisors are absent.

Tongue long and narrow, coated. Tonsils not visible. Upper arm, 28 cm. long; forearm, 22 cm. Hand relatively large; fingers of normal size. Skin of palm thick; nail-beds long but lunulæ not visible; nails not unusually fragile. Skin over elbows and knees dry, harsh, and thick. Skin of forehead thick and shiny.

Clavicles relatively large. Nipples well-developed and surrounding areolæ of pigmentation large. Breast tissue scanty.

Thorax small. Angulus sterni prominent. No marked retromanubrial dulness. Signs of infiltration of apices of lungs and of pleural effusion on the right side, with Grocco's sign on the left. Pleural tappings (Dr.

Smith) yielded turbid fluid; specific gravity, 1012 to 1017; albumin, 30 grams per liter; cell count, 640 to 860 to c.mm., nearly all small mononuclear elements.

Heart displaced to the left by the pleural effusion; pulmonic second sound markedly accentuated; no heart murmurs. Abdomen distended with bulging, dull, flanks; liver large and firm, edge palpable four finger's breadth below the costal margin in the right mammillary line; on December 23 Dr. Futcher heard a leathery friction rub over the liver; spleen also palpable two finger's breadth below the costal margin; paracentesis abdominis (Dr. Levy) yielded 2500 c.c. dark, orange-colored, turbid fluid; specific gravity, 1017; 50 grams of albumin per liter; 800 cells per c.mm., chiefly small mononuclears.

Scrotum small; left testicle in scrotum, but small, size of a large hazel nut; right testis partially undescended, palpable in groin, small. Penis fairly well developed; slight phimosis; patient asserts that he has possessed normal libido and potentia cœundi since fourteenth year. Scapulæ large. Spine normal. Feet small; wears No. 4 shoe. Pelvic measurements: Interspinous distance, 21 cm.; intercrestal distance, 22.5 cm.; intertrochanteric distance, 24.5 cm.; Baudelocque's distance (last lumbar spine to middle of upper margin of symphysis), 16 cm.

No paralyses or anesthesias; reflexes (deep and superficial) normal.

Supraclavicular gland on the right palpable; retrocervical glands and epitrochlears just palpable; other superficial lymph glands not enlarged.

Thyroid isthmus palpable; no struma; no fine tremor of fingers; no eye signs of hyperthyroidism.

Blood Examination. December 22, 1913. Red blood cells, 3,480,000; white blood cells, 2240; hemoglobin, 53 per cent.; no anisocytosis; no parasites.

January 9, 1914. White blood cells, 3400. Differential count (300 cells): Polymorphonuclear neutrophiles, 67.7 per cent.; polymorphonuclear eosinophiles, 0.3 per cent.; polymorphonuclear basophiles, 1.0 per cent.; small mononuclears, 20.7 per cent.; large mononuclears, 9.3 per cent.; transitionals, 1.0 per cent. No myelocytes; no nucleated red cells; no anisocytosis or poikilocytosis of red cells.

Urine Examination. Clear; acid; specific gravity, 1018 to 1025; trace of albumin; no sugar; microscopically a few granular casts and many amorphous urates; tests for blood and bile, negative; no acetone bodies.

Wassermann test of serum (Dr. Bloomfield) made January 2, 1914, was negative.

Ophthalmotuberculin test of Calmette (Dr. Levy) reported December 28, 1913, was negative with both 1 per cent. and 5 per cent. solution.

Feces. Examined January 12, 1914, entirely negative.

X-ray Examinations. January 10, 1914 (Dr. F. H. Baetjer). Sella turcica, normal.

Thorax, slight infiltration of both lungs; shadow at right base (effusion); shadow above heart, possibly enlarged thymus.

Temperature, Pulse, Respiration and Blood-pressure. The patient had continuous fever while in the hospital; from December 22 to December 30 it was high, varying between 100.5° and 104° F.; in the first week of January it averaged about 100° to 101°; later it rose, varying between 100° and 103° until death on January 14, 1914. Shortly before death the scleræ became icteric. The pulse rate varied between 120 and 130; the respirations between 24 and 32 per minute.

The blood-pressure was always low (70 to 90 mm. maximal systolic pressure).

Clinical Diagnosis. Tuberculous polyserositis (pleuræ; peritoneum); pulmonary tuberculosis; possibly miliary tuberculosis; cryptorchism; dwarfism; azoöspermia; hypergenitalism.

It was prophesied intra vitam that the autopsy would probably reveal well-preserved interstitial cells of Leydig in the small testicles with loss or diminution of the germinative portions of the sex-glands.

Autopsy (No. 4052). (Made in Prof. Welch's laboratory by Dr. Kline, January 14, 1914.)

Anatomical Diagnosis. Bronchial, mesenteric and retroperitoneal tuberculous adenitis; tuberculous peritonitis; subacute pleurisy; atelectasis of right lung; recent tuberculous ulcer of vocal cord; pleural and peritoneal effusions; atelectasis of right lung; miliary tubercles in lungs, liver, spleen, adrenals and kidneys; fatty liver; anemia; emaciation; jaundice; peptic duodenal ulcers; decubitus ulcers; incompletely descended testis; dwarfism.

Histological Examination of Hormonopoietic Organs (Prof. George H. Whipple).

Testicle. Uniform throughout the histological section which shows the entire gland. Both testicles were examined and were similar. The *tunica* is thickened a little and shows a little evidence of chronic inflammation. The *seminiferous tubules* are uniformly arranged, of small size, with greatly thickened basement membranes. They contain only one type of an undifferentiated cell, in general of spindle or cubical shape, with the long axis pointing toward the lumen. The nuclei are large and vesicular. The protoplasm is filmy. There are no spermatozoa. The basement membrane in places has undergone hyaline degeneration. Again the entire tubule shows a uniform, hyaline metamorphosis. There are some corpora amylaceæ probably representing deposits in degenerated tubules. Some of these show calcium impregnation.

The *bloodvessels* are not particularly thickened, but in places there is evidence of chronic inflammation, the evidence being nests of mononuclear wandering cells.

The striking thing in the sections is the uniform increase in the interstitial cells of the testicle. They are increased relatively and perhaps even absolutely. Many of them show very distinct, fine, yellow granules of pigment in their protoplasm. The nuclei stain well. Some of these masses of interstitial cells make up strands and columns as large as the shrivelled tubules.

Pancreas. The acini and islands are quite normal. There is a very slight increase in connective tissue and occasionally small inconspicuous scars are visible.

Thyroid. Colloid is quite conspicuous in all the acini, but in some it stains a very much deeper pink than in others. The acini vary greatly in size, but the lining epithelium everywhere is low, cubical in type. No hemorrhage; perhaps a slight increase in stroma. One section shows a discrete tubercle.

Adrenal. Cortex is rather thick and shows perhaps a little increase in the width of the middle zone of the cortex. The inner zone of the cortex shows considerable pigment deposit in its cell column, perhaps slightly more than normal. The medullary tissue is conspicuous and normal in appearance. The bloodvessels are engorged to a considerable extent. There are a few small scars here and there, perhaps dependent upon the general tuberculosis.

It would be interesting, did the occasion permit, to discuss the reciprocal relations of the gonads and the other endocrine glands.

In the first case reported above the inter-relations of the hypophysis cerebri and the gonads are apparent, and clinical experience indicates also a close relationship in some circumstances with the thymus, the epiphysis, the chromaffine system and the inter-renal system.

More and more we are forced to realize that the general form and the external appearance of the human body depends to a large extent upon the functioning, during the early developmental period (and later), of the endocrine glands. Our stature, the kinds of faces we have, the length of our arms and legs, the shape of the pelvis, the color and consistency of our integument, the quantity and regional location of our subcutaneous fat, the amount and distribution of hair on our bodies, the tonicity of our muscles, the sound of the voice and the size of the larynx, the emotions to which our *exterieur* gives expression—all are to a certain extent conditioned by the productivity of our hormonopoietic glands.

We are simultaneously, in a sense, the beneficiaries and the victims of the chemical correlations of our endocrine organs.

The data we are accumulating regarding these chemical correlations are not only theoretically interesting but are practically very important. More than ever before, is the minute examination of the external appearance of the body—the habitus—of significance for the practicing physician who desires to make accurate diagnoses. In this paper I have paid especial attention to the function of the gonads. It is probably no accident that, as one of the best workers in this field has expressed it, the "organs which are for the preservation of the species and the continuity of life possess (also) a modelling influence upon the individual bearer of life."

CHRONIC INTERSTITIAL GASTRITIS

By JOSEPH SAILER, M.D.
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The patient is white, aged forty-six years, a physician. His previous history is unimportant. He has been successful in his professional work. He has been very fond of outdoor life, particularly as a hunter of big game, in the pursuit of which he has spent many weeks at a time. He has indulged very moderately in alcohol and tobacco. The first of June, 1913, he was operated upon for bilateral inguinal hernia. The operation was entirely successful, the wound healed by first intention, but for some days following the operation there was intense pain in both groins. In July he noticed distinct loss of weight, and suffered from pain immediately after eating that frequently was associated with nausea. To relieve both the pain and the nausea he resorted to voluntary vomiting. In May, 1913, he weighed 178 pounds, approximately his weight for the previous ten years. In December of the same year he weighed 160 pounds. The physical examination at this time was practically negative. The thoracic organs were negative. The abdominal walls were well relaxed, facilitating palpation, but aside from the descending colon no organs were felt. There were no areas of tenderness. Loud gurgling was produced by pressure in the epigastrium. Deep pressure just above the umbilicus was slightly uncomfortable. There was no splash in the stomach two hours after taking food (glass of milk). By ausculatory percussion, the greater curvature of the stomach appeared to be at the level of the umbilicus. The nervous system was normal. An examination of the blood showed a moderate degree of anemia, 7000 white cells, and a normal differential count. The blood-pressure, 116 and 84 was slightly below normal. The gastric contents showed no free hydrochloric acid and a total acidity of 38, no occult blood, very large amount of mucus, no Oppler-Boas bacilli, and no lactic acid. There was definite evidence of peptic digestion in the diluted contents by Mette's method. The urine was normal. A diagnosis was made of severe catarrhal gastritis, the patient placed upon a careful diet and given daily lavage. This produced great subjective improvement for ten days. Then he complained of a crawling sensation in the stomach, nausea and pain after eating. His weight decreased four pounds. At this time the gastric contents obtained

two hours after a mixed test breakfast gave a total acidity of 46, no free hydrochloric. Peptic digestion was present when the contents had been diluted with $\frac{1}{20}$ normal hydrochloric acid solution. There was no occult blood, no lactic acid, no Oppler-Boas bacilli, no sarcinæ, but a great deal of squamous epithelium. During this time the patient had been on hydrochloric acid, but the last examination still failed to give free hydrochloric acid, although the total acidity had risen to 68. There was no evidence of proteid digestion and no peptic activity in the undiluted filtered stomach contents, but when diluted with $\frac{1}{20}$ normal hydrochloric acid in proportion to 1 to 16, proteid digestion was fairly active. In this specimen for the first time a large amount of pus was observed. Numerous attempts were made to obtain test meals, only a few of which were successful, because the stomach emptied itself so rapidly. All gave practically the same result, excepting the variation in the amount of total acidity. Pus was constantly present. Occult blood never. Very often, even fifteen minutes after the ingestion of food, the tube failed to obtain any of the gastric contents. An attempt was made on two occasions to obtain the duodenal contents with an Einhorn tube, but if they were obtained they corresponded in all respects to the gastric contents, and nothing was learned excepting that in the supposed duodenal contents trypsin could not be demonstrated. Early in January, Dr. Miller, of the German Hospital, took two *x*-rays that were very clear and definite. They showed that the lumen of the stomach was very much reduced in size, was distinctly irregular in outline, and a diagnosis of linitis plastica was made. Subsequently fluoroscopic studies were made by Dr. H. K. Pancoast, at the University Hospital. These confirmed the findings of Dr. Miller, indicating greatly thickened gastric walls, and with the fluoroscope a most extraordinary degree of gastric hypermotility was observed. This was not hypermotility due to excessive peristalsis, but rather to the fact that the bismuth flowed through the rigid tube formed by the thickened stomach walls, almost immediately into the duodenum. The patient lost weight for a time, until he reached a minimum of 139 net. Later assimulation seemed to improve and at one time his weight increased to 149 pounds, but averaged approximately 145 pounds. There was otherwise no change in his condition excepting that from time to time some tenderness could be obtained just to the right of the median line in the costal margin, and occasionally a mass could be felt which seemed to correspond to the rounded greater curvature of the stomach. This could only be felt on deep inspiration, and was not constantly present. In view of the pus, it was suspected that there might be some infectious process in the wall of the stomach, and Dr. Damon R. Pfeiffer performed a series of agglutination tests with all the microörganisms that he happened to have in the pathological laboratory of the German Hospital, amounting to about twenty. These included all

the ordinary pyogenic organisms, colon, typhoid, and the various strains of paratyphoid, but all were negative. Several hypodermic injections of theosinamin were made without definite results, although the patient complained of a distinct sensation in the region of the stomach and also, somewhat unexpectedly, in the inguinal operation wounds immediately

after the injections. There was no evidence of improvement and they were discontinued. It was therefore decided to perform an exploratory operation which had not been done earlier, partly because there was no evidence of obstruction in the gastrointestinal tract and partly because the surgeon consultants had advised against it. However, they were persuaded. The operation was merely an inspection of the abdominal

viscera which confirmed the clinical diagnosis and the abdomen was then closed. The surgeons were very positive that the condition was cancerous. There was, however, in spite of careful search, no evidence of metastases. There were no enlarged glands along the lesser curvature. There were some masses around the greater curvature that were probably enlarged lymph glands. There were some very slight adhesions around the pylorus, which were separated, and the great omentum was adherent to the wall of the abdomen apparently close to the site of the operation for hernia. The patient made a prompt and satisfactory recovery, and is now, five months later, in as good condition as he was before.

This case presents certain interesting and unusual features. First, the development of symptoms one month after the operation for hernia raises the question whether the latter could have had anything to do with the subsequent gastric condition. If it had there is no possible way of demonstrating the fact. There was not at the time nor at the subsequent operation aside from the omental adhesions any evidence of infection of the hernial wounds. Second, the persistent patulous condition of the pylorus is unusual for, with one exception, in all cases hitherto reported obstruction and retention of the gastric contents have been present. Third, the persistent absence of free hydrochloric acid, even although the total acidity reached 68, is somewhat difficult to explain. Fourth the fact that pepsin was undoubtedly secreted, although in the absence of free hydrochloric acid it did not act upon the proteid ingested. It always became active as soon as the gastric contents were diluted with hydrochloric acid solution. Pus was frequently found at first; occult or visible blood never; lactic acid never, and although it has been observed in some of the recorded cases, it is not constant and probably only occurs when there is stagnation of the gastric contents.

The really important feature of this case was the difference of opinion of the surgeons on the one hand and the medical men on the other. The surgeons declared positively that the growth in the stomach was of a cancerous nature, and therefore refused to take any radical procedure whatever that offered even a remote chance for permanent improvement. The medical men took the view that the cancerous nature of all of these cases has not been sufficiently demonstrated, and therefore urged any reasonable

attempt either to remove the lower part of the stomach, which was the part most affected, or to provide for a permanently patulous intestinal tract if, as seemed not unlikely, the continued contraction of the lower part ultimately resulted in partial or complete obstruction. The patient shared very earnestly the views of the internists and was willing to run any risk in the hope either of shortening his life or of prolonging it indefinitely.

The names of this condition are numerous and all more or less descriptive; leather-bottle stomach, Schrumpfmagen; hypertrophic gastritis (Cruveilhier); chronic indurative sclerosis of the pylorus, cirrhosis of the stomach, linitis plastica (Brinton); fibroid induration, sclerosis are sufficiently indicative of the fact that the wall of the stomach is thickened and hard. Although Luther, Cruveilhier, Andral, and others had called attention to the existence of this condition earlier, William Brinton was the first to regard it seriously as an independent disease. He devotes a chapter to it in his lectures on diseases of the stomach. He describes two forms, that of contraction and the rarer form of dilatation, and expressed the belief that in a partial form the condition was fairly common, a belief that further experience has not confirmed. He cites no case, but must personally have seen several and for various reasons, given chiefly in a footnote, prefers the name linitis plastica to any other designation. The next important article was that of Hanot and Gombault in 1882, who reported one case and analyzed the literature. This was followed in 1893 by Tilger, who also reported a case and collected all certain cases previously reported in the literature. His own case occurred in a woman, aged thirty-five years, who had a dilated stomach and an obstruction of the pylorus. An attempt to operate was futile on account of the desperate condition of the patient, and she died the following day. Codivilla collected twenty-three cases, all of which died and in which the diagnosis was confirmed by autopsy. Of these thirteen were men and ten were women and the ages ranged pretty regularly from twenty to seventy. He denies very earnestly a carcinomatous nature of the condition. In a postscript he mentions a case reported in which a correct diagnosis was made during life and a digital devulsion twice practised with cure. Subsequently Einhorn reported four operative cases with cure and

Hemmeter in his text book, which contains a very excellent article on this subject, reports two fatal cases and mentions the fact that he has also seen two others. In 1907 von Sury reported a case from the Pathological Anatomical Institute of the University of Basle, with very careful histological study. He defines the condition as follows: (1) A primary more or less extensive increase in the thickness of the wall of the stomach as a result of new formed connective tissue, particularly in the submucosa and subserosa. (2) A diminution in the size of the stomach as a result of secondary contraction. This is usually the result of an existing or completed inflammation of the wall of the stomach. He also gives a brief clinical picture of the disease, of which the most interesting features are the frequency of ascites and the fact that a tumor can usually sooner or later be felt in the epigastrium. The duration is from three to five years. It occurs in early as well as in late life and there are neither metastases nor hematamesis. All these features distinguish the condition from carcinoma. The surgical treatment is the most important. He is rather inclined to group it with fibrous polyserositis, either the form described by Pick or the iced liver of Curschmann. One hundred and seventy-two references to the literature, the largest collection hitherto made, are appended to this article. In 1898 Boas reported three characteristic cases of this condition, all of which had been cured by gastroenterostomy. They were all of the obstructive type. It must be admitted that in none of these cases was the subsequent history known for a sufficiently long time to exclude the possibility of a carcinomatous change. Quenu in 1908 reported two cases of gastrectomy for this condition. The man lived two years, and then died of hemorrhagic pleurisy, probably carcinomatous. The woman lived two and one-half years and died of a local return. In both cases the histological examination indicated the carcinomatous nature of the process. Münter, in discussing four cases of this condition, reached a conclusion that there are several forms of chronic gastritis.

The question of the true nature of this condition has been agitated very much since it was first recognized. There have been those who held it was carcinomatous in nature and others, like Tilger and von Sury, who believed that it was a chronic interstitial process. It had

been my hope when I presented the title of this paper to be able to discuss this subject from the standpoint of a careful histological examination of the tissues. It had been decided at that time to operate, and it was the expectation of all that a partial gastrectomy would be performed. As the history has shown this expectation was not fulfilled. It is, however, my opinion that the question of the exact nature of this process is from a clinical standpoint unimportant. Souper has recently reported an exceedingly interesting case correctly diagnosed which was of the common form associated with stenosis of the pylorus, and the patient three years after the operation was apparently perfectly well. As Souper very sensibly remarks the possibility of carcinoma is probably not to be considered now. Dr. David Riesman recently reported a case, as yet unpublished, before the Musser Clinical Club. The patient is alive and in good health five years after a gastroenterostomy. It seems to me therefore clear that not all of these cases can be carcinomatous, although the two cases of Quenu suggest that at least some of them are, and in this state of uncertainty it is important to treat every case as if it were benign. Bland-Sutton in a recent excellent article on this subject is somewhat undecided in his views and inclined to think that many of the cases are not malignant in nature. To my mind one of the most difficult tasks in morbid histology is the differentiation of a chronic sclerosing inflammation of a mucous membrane from carcinoma. The pictures presented by the two conditions are often similar to a puzzling degree, and I should be loathe to rely upon the histological evidence of the stomach wall alone unsupported by demonstrated epithelial metastases in the lymph glands or in other organs.

Certain features of this case appear to justify its report at the present time. They are as follows:

1. The occurrence of the symptoms about one month after an operation for bilateral inguinal hernia. Only the sequence of the two events leads to any suspicion that they are associated.

2. The fact that this case differs from almost all of the recorded cases in not presenting any stenotic features. One case recorded by Jonas seemed to display the same rapid emptying of the stomach. This must not be regarded as hypermotility, because there was no

evidence of peristaltic activity in the gastric wall and it is quite impossible to suppose that any such activity could have existed. It merely means a permanently patulous pylorus. This condition actually produced a difficult complication. At first we were unwilling to operate because nearly all previous operations on these cases had consisted of a gastroenterostomy and obviously gastroenterostomy was not required in a case in which the stomach rapidly emptied itself into the duodenum. It was an additional reason why nothing was attempted at the exploratory operation above described. Some hitherto untried operative procedure is probably necessary in a case of this kind.

3. The distinct evidence of some focus of suppuration apparently of a transient character. Pus was not found at first nor has it been found lately, but in the interval formed a considerable and characteristic portion of the gastric contents. This confirms the view of Bland-Sutton that gastric ulcer is the most frequent cause.

4. The absence of lactic acid from the stomach contents. This has been reported in many cases, but in these was almost certainly the result of retention of the stomach contents. As they were not retained in this case, lactic acid did not appear.

5. The evidence at the time of operation that the process had begun in the pyloric region. The wall in this region was distinctly thicker, somewhat harder, and appeared more altered than the remaining portion of the stomach, although the thickening of the gastric walls extended as far as the fundus.

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DISCUSSION

Dr. David Riesman: The *x*-ray, while it shows the leather-bottle stomach, unfortunately does not enable us to distinguish between the malignant and the non-malignant types. Such distinction, and it is an important one, can only be made by clinical observation. Thus, I saw a case recently that was a typical leather-bottle stomach which, however, proved to be malignant, the patient rapidly developing cachexia and ascites, and dying in a few weeks. There was no evidence during life of metastasis to the liver. An autopsy was not obtained. In another case that did come to autopsy metastasis to the viscera was absent, but there was marked enlargement of the lymph glands along the greater curvature of the stomach.

The case to which Dr. Sailer referred came under my care five years ago. He had lost enormously in weight, vomited everything he ingested, and suffered much from epigastric pain. I do not recall the results of the test meal, but believe there was anacidity. I did not think the condition was malignant on account of the long duration. At operation it was found that the stomach had been converted into a thick-walled cylinder about the size of the large intestine. With difficulty the cardiac end and the small bowel were united, the stomach being left *in situ*. The operation, which was performed by Dr. F. T. Stewart, was entirely successful, and the patient is alive and well, barring certain idiosyncrasies as to food. In this patient there was a history of syphilis and this may have been a factor in the production of the fibrous linitis. I am sure that at operation it may be difficult to tell whether the condition is sarcomatous, carcinomatous or merely fibrous. Enlargement of the glands is suggestive of malignancy.

THE SUBCUTANEOUS INJECTION OF OXYGEN AS A THERAPEUTIC MEASURE

By JOHN McCRAE, M.D., M.R.C.P.
MONTREAL

In 1912 Derose[1] published an account of a method of injecting oxygen subcutaneously, as being preferable in some cases to the older method of its use by inhalation. It has been the experience of many physicians to finally lose faith in the stimulant and life-saving powers of oxygen, because again and again the appearance of the oxygen tank merely meant that the death of the patient was imminent. Evidently Derose's announcement created no marked interest, although from time to time notice appeared of the use of the method in a casual way. My own attention was called to the procedure by Dr. Henry O. Howitt, of Guelph, Ontario, who read a paper in July, 1913, at the Canadian Medical Association, upon the results he had obtained by its use. Early in his experience he was so fortunate as to resuscitate a patient whom he thought to be beyond the possibility of recovery, and after a protracted and somewhat disappointing experience of it in hospital practice, a similar result happened in my own work.

Observations appearing in medical literature appear to indicate that the method has been used more in France than elsewhere. In August, 1912, Williams tried the effect of intramammary injection of oxygen gas with an indefinite idea of following the procedure of injecting oxygen into the udders of cows suffering from milk fever. The method was used for the relief of eclampsia, and, reading the author's description, one concludes that the injection was largely into the tissues of the breast rather than into the ducts. Good effects were obtained which the author himself attributes as much to the absorption of oxygen in a general way from the tissues as to

[1] The Subcutaneous Injection of Oxygen; Its Indications, Technique, and Results, Med. Press and Circ. London, 1912, n. s., xciii, 459.

any specific effect upon the eclamptic state. Bayeux[1] treated pulmonary tuberculosis and its consequent breathlessness by a series of injections—twenty in three months—of oxygen into the tissues, with the result that he has a decided predilection in favor of its use. Delmas and Delmas[2] detail their experience of its use in the resuscitation of asphyxiated newborn infants, using the gas produced from the action of water on sodium peroxide. The gas was injected into the breast until a lump the size of an orange was raised, and the results were good.

Derose's method is to employ a metal cylinder, closed by a heavy metal top, which is clamped down; from the cylinder an opening with a tube permits the oxygen to escape. A gauge at the side allows the eye to estimate the pressure of the gas in the cylinder; a block of sodium peroxide immersed in water supplies the gas, of which it is estimated that 2 liters are supplied from 10 grams of the chemical. The gas runs at a low pressure into the tissues, and the treatment may be continued for a considerable time. Sodium hydroxide is commercially supplied in tins, one tin for each series of injections; holes are punched in the tin immediately before it is immersed in the water.

The method I have used consists in conducting the gas from the usual high-pressure oxygen cylinder in every-day use. To the cylinder is attached the usual valve and wheel by which the escape of the gas is regulated. Rubber tubing, about 1 cm. in diameter, and a small needle completes the equipment. The needles supplied with antitoxin answer very well. The whole is clean, the needle sterilized; tincture of iodin is applied to the skin at any desired part, usually the upper thorax; any part of the body where the skin is lax will do equally well. The needle is placed under the surface of alcohol or sterile water so that the rate of flow may be observed. Just short of a continuous stream of bubbles answers best, although the rate does not appear to be of much moment. The needle is then pushed through the skin and according to the less or greater depth to which it reaches, the oxygen will be seen

[1] Traitément de la tuberculose pulmonaire par les injections hypodermiques de gaz oxygène, Ann. de méd. et chir. inf., Paris, 1912, xvi, 337–344.

[2] Sur l'emploi de l'oxygène pur comme traitément de la mort apparente du nouveau-né, Rev. mens. de gynéc., d'obstet. et de pediat., Paris, 1912, vii, 245.

infiltrating in all directions, or a gradually increasing lump rises. Without being able to measure the amount accurately, the usual procedure is to raise a lump of half the size of a foot-ball, thirty seconds or a minute being sufficient time for this amount. If the needle be withdrawn and the opening stopped by a piece of adhesive plaster, it will be noted that absorption usually occurs quickly, in a few minutes the mass will have disappeared, although for several hours the fingers can detect crepitation over the spot; with the stethoscope loud crackles may be heard for a couple of days. The distending process, even where it has been fairly sudden, has never in my experience excited any comment from the patient upon its painfulness.

Many modifications of this mode were used: with the idea of purifying the oxygen, it was bubbled through water, with the result that air-emphysema followed; a rubber bag filled from time to time from the tank seemed to give no advantage, and sometimes the pressure seemed unnecessarily low when it was employed.

Oxygen was applied in this manner to some 33 patients with different diseases; the striking case alluded to above was that of a man, aged thirty years, who, after resection of a large piece of bowel and new growth, appeared to be dying three hours after operation; the lungs were greatly edematous, respirations sixty to the minute, and very shallow; my impression was that he would die within a quarter of an hour. He was given four large injections during three hours and lived. Although no alteration was noted for a considerable time in the rate of respiration, his comfort increased from the moment the gas was applied.

In cardiac and renal dyspnea the comfort obtained was usually notable: in one case of cardiac disease, where severe dyspnea was met repeatedly by the use of morphin, we were able for several days to replace the morphin entirely by oxygen.

Eleven cases of pneumonia were repeatedly treated, and the results were extremely disappointing. The respiration rate never decreased by more than six per minute, and the rate often remained unchanged. It is true that comfort was at times increased, and cyanosis sometimes lessened; the course of the disease appeared totally unaffected. Such a result might be predicted, if one bears

in mind Peabody's[1] observation that in pneumococcus bacteriemia, the oxygen-combining power of the blood falls with the progress of the disease. A recent paper dealing with uses of oxygen in tissue mechanism and its relation to respiration, by A. G. Auld[2] will repay reading.

Without making any claims whatever on behalf of oxygen gas thus administered, it remains to be said that here is an easy method of administration in which there is no waste, and in which presumably the oxygen is used as it is needed by the corpuscles and the tissues; further, in cases where respiration is interfered with or is in abeyance, it may quickly be given, and in as many parts of the body in quick succession as is desired. It seems a desirable addition to the armament of the operating-room as a provision against accidents of anesthesia, the more so as it can be administered by a nurse without interfering with those who are concerned, for the moment, in other active measures.

By way of summary, the following states were proved to be amenable to its use:

1. Accidents from anesthesia.
2. Edema of the lungs, edema of the glottis, and accidental interference with respiration by disease of the upper part of the respiratory tract.
3. Marked dyspnea with defective oxygenation, as in cardiac and renal disease.
4. Asphyxia of infants at birth.
5. Syncope.
6. Electrocution.

DISCUSSION

DR. MELTZER: I might perhaps mention here some experiments which we have never put on record. Fifteen years ago Dr. Gies and I made some studies on animals trying to see whether subcutaneous injections of oxygen could relieve dyspnea and asphyxia. I shall not enter into details. I shall merely say that the emphysema produced by the oxygen rather hastened the death of the animals.

[1] The Carbon Dioxide Content of the Blood in Pneumonia, Jour. Exper. Med., 1912, xvi, 701.

[2] Oxygen Want and the Means of its Relief, British Med. Jour., 1914, i, 1060.

THE RELATION OF GLYCOSURIA TO PITUITARY DISEASE AND THE REPORT OF A CASE, WITH STATISTICS

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AND

H. LEON JAMESON, M.D.

PHILADELPHIA

The extraordinary influence of the pituitary gland upon the metabolism and development of the body is now universally conceded. Cushing[1] has grouped the disturbances of the hypophysis cerebri under the term "dyspituitarism," the manifestations being due partly to primary involvement of the gland and partly to the effects of pressure upon neighboring structures.[2] That pituitary disease, however, occasions secondary alterations in the functions of certain internal secretions is quite probable. In support of the fact that hyperthyroidism may be consequential to lesions of the hypophysis, we desire to report a case of acromegaly with glycosuria in which there were manifestations of exophthalmic goitre.

The patient, A. H., aged forty-six years, occupation cook, weight 170 pounds, and height 5 feet 9½ inches, first fell under the care of my surgical colleague, Dr. William L. Rodman, in the Medico-Chirurgical Hospital, at which time she was suffering from a gangrenous wound, inflicted by a fish bone, of the left hand. On December 12, 1913 (a few days later), the patient was referred to the medical service—to us—for study and treatment. It should be stated at the outset that the left hand continued to show swelling, was very painful, and presented a large gangrenous ulcer on the palmar surface of the index and middle fingers, with slow extension

until death occurred. Polydipsia, polyuria, and glycosuria, as well as bulimia, were all prominent features throughout the illness. The percentage of sugar at first was 5 per cent., but at the end of one week it rose gradually to 7 per cent., and remained at this level until the end.

The typical symptoms of acromegaly were in evidence, as the accompanying photographs would also indicate. The hypertrophy involved both the bones, especially of the face, hands, and feet, and the soft parts, the lips being much thickened. According to the history the bones of the hands and face began to enlarge four years ago, while the glycosuria set in about two years later. An *x*-ray examination by Dr. George E. Pfahler showed marked lipping at the edges of the articular surfaces of the metacarpal bones and phalanges, such as is found in acromegaly, and also a tumor of the pituitary gland, with absorption of the clinoid processes.

The diagnosis of associated hyperthyroidism was quite apparent from the noticeable enlargement of the thyroid gland, together with tremor, tachycardia, and exophthalmos. The goitre was bilateral, although asymmetrical, soft, and elastic, but gave no suggestion of fluctuation. On auscultation a systolic arterial murmur was heard over the larger right lobe of the thyroid gland. The exophthalmos, although moderate in degree, was, as is the rule, an obtrusive symptom. The indications of exophthalmic goitre were most probably developed after the glycosuria had existed for an indefinite period of time, although being, as is usual, of insidious origin, it was impossible to fix the precise date of onset.

The Wassermann reaction gave a negative result. Two weeks prior to the fatal termination, bed-sores developed, and despite our best efforts to arrest them, became extensive and contributed to the gradually increasing exhaustion until the end was reached. During the twenty-four hours preceding death, coma, from which it was impossible to arouse the patient, developed. Death occurred on January 16, 1914. No autopsy was permitted.

Marinesco[3] reports a case showing, similarly, the association of acromegaly, diabetes mellitus, and certain unmistakable indications

of Basedow's syndrome. Etiological significance in the production of hyperthyroidism has been attributed to acromegaly, but the nature of the relationship is not perfectly understood. Dock states that the diabetes arising in the course of acromegaly is cerebral and due to the pituitary disease, as shown by the fact that "diabetes is most marked with the largest tumors,"[4] an observation confirmed by our studies. According to Borchardt[5] this dictum is also corroborated by experiments on animals.

FIG. 1.—Showing hypertrophy of bones of face, characteristic of acromegaly.

The metabolic changes caused by acromegaly are inconstant. Borchardt[6] in reports of 176 cases found diabetes recorded in 63 or 35.8 per cent., and alimentary glycosuria in 8 more. J. H. W. Rhein[7] studied in the literature the symptomatology of 169 cases of tumor of the hypophysis and found glycosuria in only 7, or 4.1 per cent. Among these, 52 instances of acromegaly, or 30.8 per cent., occurred.

The purpose of the present statistical investigations has been to collect all of the cases of pituitary disease recorded in literature since the publication of the paper by Borchardt, or, in other words, a period of five years terminating December 31, 1913; also to either confirm or refute certain views which have been advanced in the past, notably that by Kollaritz,[8] that glycosuria does not occur in tumors of the hypophysis without associated acromegaly. Again, it was hoped that the facts and data thus gleaned might aid in clearing up the question of the relation of hypo- and hyperthyroidism to acromegaly on the one hand and glycosuria on the other.

FIG. 2.—Hypertrophy of bones of hand typical of acromegaly.

Our collective investigations yielded a total of 246 cases of hypophysial disease. In 183 cases the urinary findings were mentioned and showed 28 instances of glycosuria, in 9 of which the condition was intermittent, and the subjoined table represents an analysis of these cases.

It will be observed from the accompanying table that 16 of the 28 cases of pituitary glycosuria, or 57.1 per cent., showed acromegaly, while 10, or 35.7 per cent. failed to show the latter condition in association. In 2 cases the presence of acromegaly was in doubt, hence excluded. It is interesting to note that of the 183 cases of pituitary disease in which the urinary findings were given, 88, or 42.6 per cent. showed acromegaly, and of the latter only 16, or 18.2 per cent. showed the presence of sugar. Moreover, it is a matter of no less interest that in 91 cases of pituitary disease in which acromegaly was absent, 10 showed spontaneous glycosuria, and no mention was made of either hypo- or hyperthyroidism in these cases.

The foregoing facts are not in accord with the observations of Kollaritz,[9] who recorded 52 cases of tumor of the hypophysis without acromegaly, of which not one was complicated by diabetes. Borchardt, writing in 1908, also affirms that since 1886 not one case of tumor without acromegaly was found in which glycosuria was associated. Sainton and Rol[10] state that although pituitary glycosuria without acromegaly may occur, it is rare. Here it is to be recollected that when spontaneous glycosuria is absent from this tripod of conditions, experimental observation may show the presence of an alimentary glycosuria. For example, Borchardt[11] reports 10 cases of acromegaly without spontaneous glycosuria, of which 8 showed the alimentary form, applying the usual test. He claims that glycosuria in one of its forms is more regularly present in acromegaly than in any other disease.

As an examination of the accompanying table with reference to the hypophysial lesions will show, there was tumor in 72 cases (of which 3 were specified as sarcoma, 2 as cyst, 1 adenocarcinoma, 1 epithelioma, 1 adenoma, and 4 as "tumor"), tuberculosis in 3, gumma in 2, hypertrophy in 1, fracture at base of skull with extravasated blood in 1, and lesion not stated in 8. The ages in our series were given in 21 cases, out of the total of 28, and found to average thirty-seven and one-quarter years, the period of life intervening between twenty-five and sixty years furnishing all save 3 cases.

Author.	Age and sex.	Lesions of pituitary.	Acromegaly.	Glycosuria.	Other ductless glands.	Remarks.
Cushing[16]	36 yrs. F.	?	Absent (hypopituitarism)	Glycosuria, intermittent Polyuria, constant	No mention	
Cushing[17]	40 yrs. M.	Tubercle of pars-anterior	Absent	Glycosuria, intermittent Polyuria constant	No mention	Glycosuria developed one year after operation.
Kocher[18]	30 yrs. F.	Sarcoma	Present	Diabetes, persistent	Thyroid, small Thymus, persistent	Patient operated upon.
Lucien and Parisot[19]	65 yrs. F.	Tuberculosis	Absent	200 to 300 gms. in 24 hrs.	.....	Pulmonary tuberculosis; pancreas normal.
Shoemaker[20]	35 yrs. F.	Adenocarcinoma	No mention	Glycosuria shortly before death	Thyroids and adrenals, normal	Bitemporal hemianopsia.
Messedaglia[21]	...	.....	Present	Glycosuria preceded hypophysial symptoms		
Church[22]	14 yrs. M.	Hemorrhagic cyst	Absent (infantilism)	Diabetes at 3½ yrs., duration not stated	No mention	Right temporal hemianopsia.
W. Romelaere[23]	...	Sarcoma	Present	Diabetes mellitus	Cirrhosis of pancreas and suprarenal glands	Blind. Death from bronchopneumonia.
Launois and Cleret[24]	33 yrs. F.	Sarcoma	Absent (hypopituitarism)	Diabetes mellitus	.....	Bilateral hemianopsia, mental torpor.
Moskalew[25]	52 yrs. F.	Epithelioma	Absent	1 to 4.5 per cent. sugar		
Foucault[26]	?	Tuberculosis	?	Diabetes mellitus	?	Thesis inaccessible.
Goldscheider[27]	51 yrs. F.	No tumor; assumes hypophysial alteration	Present	6 to 8 per cent. of sugar	Right ovary missing; thyroid and other ductless glands not mentioned	Glandular extracts had no effect. Exophthalmos present.
Marek[28]	26 yrs. F.	.....	Present	Began eighth month of pregnancy, disappeared after delivery	No mention	Primapara developed acromegaly late in pregnancy.
Echevarria[29]	...	?	Present	Diabetes mellitus	.....	Paper inaccessible.
Medigreceanu and Kristeller[30]	28 yrs. M.		Present	100 to 150 gms. per day; later increased tolerance		
Goetsch, Cushing and Jacobson[31]	...	.....	Present	Glycosuria, later increased tolerance		
Bittorf[32]	38 yrs. M.	Tumor (gumma?)	Present	Alimentary glycosuria	Thyroid normal	Binasal hemianopsia, Wassermann positive.
Amsler[33]	41 yrs. M.	Tumor	Present	Diabetes mellitus during acromegaly	Hyperplasia of spleen, pancreas and adrenals	Arteriosclerosis present.
Cushing[34]	32 yrs. M.	Gumma of pars-anterior and intermedia	Absent	Glycosuria disappeared; polyuria persisted	No mention	Slight exophthalmos.
Fisher[35]	29 yrs. M.	Fracture at base of skull	Absent	Glycosuria, intermittent first, 24 hrs. after fall	No mention	Glycosuria attributed to irritation of posterior lobe by extravasated blood.
Hill[36]	18 yrs. M.	Cyst	Absent (Frohlich's syndrome)	Marked polyuria. Glycosuria cleared after operation	Thyroid and thymus not palpable	Operation caused marked improvement. Attributed glycosuria to intracranial pressure.

Author.	Age and sex.	Lesions of pituitary.	Acromegaly.	Glycosuria.	Other ductless glands.	Remarks.
Carnot, Rathery and Dumont[37]	58 yrs. F.	Hypertrophy	Present	80 to 295 gms. in 24 hrs.	Thyroid sclerotic and cystic; suprarenals and pancreas sclerotic and hemorrhagic; ovaries sclerotic	
Fink[38]	...	?	Present	Diabetes mellitus	?	Dissertation inaccessible.
Sainton and Roi[39]	16 yrs. F.	Tumor probably malignant	Absent	Diabetes of grave juvenile type	Thyroid atrophied and sclerotic	Bilateral hemianopsia; knee-jerks exaggerated; speech slow.
Genella[40]	45 yrs. M.	Probable tumor	Present (atypical)	Glucose, 3 to 5 per cent.	.....	Difficulty in speech; reflexes diminished.
Meyer[41]	...	.....	Present	Diabetes mellitus	.....	Associated with paranoia.
Grinker[42]	49 yrs. M.	Adenoma	Present	Intermittent and slight	Thyroid not palpable	Subject to epileptic attacks.
Anders and Jameson	46 yrs. F.	Tumor	Present	Persistently present, 5 to 7 per cent.	Well-marked evidence of hyperthyroidism	Gangrene of hand. No hemianopsia.

In view of the fact that glycosuria not uncommonly complicates exophthalmic goitre, the question naturally arises whether in a case such as reported above it is to be attributed to the associated hyperthyroidism or to the hypophysial disease. As the result of the present investigations into the literature of the subject covering five years which ended January 1, 1914, there was but 1 case of hyperthyroidism in combination with pituitary lesions and glycosuria, out of a total of 28 cases recorded, namely, our own case herein reported, so that the role played by the thyroid gland in the causation of glycosuria in these cases would appear to be both trivial and obscure.

Cushing[12] states that in none of his 26 cases were there any symptomatic evidences of hyperthyroidism, but he found some degree of exophthalmos, which in all probability was a neighborhood effect of the tumor, to be common. On the other hand, Exner[13] refers to two of Hochenegg's patients with acromegaly and partial glandular extirpation, in which subsequent enlargement of the thyroid, occurred. It is highly probable that the results of various observers will not be in agreement on the point at issue for the reason that some of the cases are studied in the stage of insufficiency while others are investigated in that of hyperthyroidism.

The balance of evidence—experimental, pathological, clinical—is in favor of the view that insufficiency of the thyroid gland increases carbohydrate tolerance. A. Lorand[14] believes that thyroidism is the dominating cause of the glycosuria in the rare cases in which pituitary disease and glycosuria coexist with Graves' disease.

Furnival found only 5 thyroids which could be considered normal out of 24 cases of acromegaly. Conversely, Schoneman's[15] studies of the pituitary body in 85 cases of goitre revealed marked alterations in all but one instance. In this connection two facts pointed out by Cushing are worthy of note: (1) that the two glands have some histological points of resemblance, and (2) that both have a somewhat similar influence on skeletal growth. Microscopic changes in the thyroid in cases of acromegaly are for the most part a low epithelium with excess of colloid.

As pointed out by Cushing, care must be exercised not to confuse mere exophthalmos due to neighborhood pressure with associated exophthalmic goitre. For example, there were 2 cases of simple exophthalmos, the result of mechanical pressure, and only 1 of associated Graves' disease in our series of 28 cases.

In concluding, there are two hypotheses pertaining to the combined conditions discussed above which have received considerable corroborative support from our statistical inquiries: (1) that the relationship existing between hyperthyroidism and pituitary glycosuria, with or without acromegaly, is a remote one, and (2) that pituitary glycosuria without acromegaly not uncommonly occurs (in 10 of our series, as against 16 in which acromegaly was also associated) contrary to the opinions of certain writers.

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DISCUSSION

Dr. Thomas B. Futcher: Dr. Anders' case brings up the question of the relationship between carbohydrate metabolism and the functions of the internal secretions of the ductless glands. It is well known that cases of caromegaly are associated with disease of the anterior lobe of the gland, and that the posterior lobe influences carbohydrate assimilation. It is generally believed at the present time that in the early stages of acromegaly, if one tests the urine, one will nearly always find a lowered carbohydrate tolerance or even an actual glycosuria, whereas in the later stages there is an increased carbohydrate tolerance. What takes place is this: In the early stages of acromegaly the affection of the anterior lobe which causes

the skeletal and other changes produces a stimulation of the functions of the posterior lobe. The increased posterior lobe secretion is supposed to inhibit the restraining influence of the pancreatic hormone on glycogenolysis. Hyperglycogenolysis and hyperglycemia, with consequent glycosuria result. In the later stages, the tumor or cyst of the anterior lobe causes atrophy of the posterior lobe by compression and hypopituitarism follows. Consequently the posterior lobe secretion becomes deficient or absent and the inhibiting influence of this secretion on the pancreatic hormone is withdrawn, so that there is nothing to counteract the restraining influence of the pancreatic hormone on glycogenolysis. Therefore, in the late stages we get hypoglycogenolysis and consequent increased carbohydrate tolerance, with absence of sugar in the urine.

If the urine of all cases of acromegaly were followed from the beginning, it is probable that a diminished tolerance for carbohydrates, or an actual glycosuria, would be found in the early stages, whereas an increased tolerance and no glycosuria would be revealed in the later stages. The discrepancies in the urinary findings in acromegaly are therefore largely due to the stage of the disease during which the observations are made.

Dr. A. S. Warthin: In connection with the subject under consideration I would like to call the attention of the association to some remarkable observations in cases of pituitary disease that have not yet been recorded. I refer particularly to the extraordinary increase in body temperature after death. In two cases of pituitary disease observed at Ann Arbor in which there was undoubted destruction of the anterior lobe, with a positive result, the postmortem axillary temperature seven hours after death was 103° to 104°; the rectal temperature in one was 106°, and in the other 108°. In spite of the abdomen being open and the fact that the body lay upon an autopsy table over which cold water was running the temperature kept up. While the abdomen was open a relatively uniform temperature kept up, but the temperature seemed to localize itself in the adipose tissue. A large portion of the fat abdominal wall was removed and kept outside, and according to the thermometer, it showed a temperature of 103° for more than eight hours after its removal from the body.

X-RAY EVIDENCE IN EARLY AND LATENT CANCER OF THE STOMACH

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Medical literature is filled with accurate descriptions and beautiful *x*-ray pictures of late cancer, but we all know that many cases of early cancer and many cases of latent cancer have escaped detection by former clinical methods. The present study was made to find out how far the *x*-rays is helping to discover these early and latent cases. The early symptoms and chemical changes due to gastric cancer are often vague. We hoped to find that the early anatomical changes in the stomach wall, which could be detected by the *x*-rays, would prove to be more definite and characteristic.

The patients are recent ones in order to make the most of recent improvements in *x*-ray technique. They were carefully studied by other methods of diagnosis.

The diagnosis of cancer was verified by operation, autopsy, or an unmistakable course. Most cases in which cancer was ruled out have been followed to operation or for six months or more after examination to verify the diagnosis as far as possible.

The material for this study consists of 114 hospital and private cases, examined within a year and a half by clinical and *x*-ray methods, in which cancer of the stomach was suspected or found.

In 40 cases cancer was ultimately proved and in 66 ultimately ruled out, 8 remain doubtful at present; 33 cases of cancer are excluded from this paper as being well developed, leaving 81 early, latent, or suspected cases. These 81 cases were classed at the end of our clinical and *x*-ray examination as follows: 1 (or 2) early; 6 latent; 62 ruled out; 12 (or 11) doubtful. In all cases a complete physical examination was made, usually including tests of secretion and motility of the stomach, and an examination of the feces and gastric contents for blood. With the *x*-rays both fluoroscope and plates were used, immediately after a bismuth meal, and at six and twenty-four-hour intervals.

In 33 cases of proved cancer the diagnosis was definitely made by the well-known signs and symptoms, and the *x*-ray examination was merely confirmatory. The remaining group of 7 cases of proved cancers, though small, is very interesting, and represents either early or latent cancer. Many cases of cancer are called latent in general practice, because no thorough examination of the stomach is made. When examination is made they are readily discovered. There is another group which are truly latent, the cases which remain hidden or very doubtful even after careful clinical examination of the stomach, and which may be first demonstrated clearly by the *x*-rays.

The percentage of these doubtful and difficult cases is rather high in this series, as they are the ones which were most frequently seen in consultation and most frequently chosen for *x*-ray examination at the hospital.

Technical Evidence. The direct demonstration of the cancer itself is of far more value than indirect evidence, such as motility and residue.

The most important evidence is a constant defect in the outline of the stomach on filling it with bismuth. In the very earliest cases this is due to a slight local thickening, with disturbed peristalsis, and hard or impossible to recognize as cancer. In later cases the defect is irregular in outline and of any size, and looks like a jagged bite out of the stomach shadow. It may be annular at the pylorus and extending upward, making the stomach funnel-shaped with a long narrow canal. The shadow may have a worm-

eaten appearance. There is usually rigidity of the wall and local absence of peristalsis.

Scirrhous growth may thicken the wall without projecting into it, making a "leather-bottle" stomach with little or no peristalsis and high position in the abdomen.

The stomach usually empties rapidly in the latent cases. This is usually due to the relaxed pylorus found with low secretion, or occasionally to a rigid, open pylorus, involved in cancer.

If the pylorus is obstructed the stomach empties slowly. Such cases may be confused with ulcer or adhesions about the pylorus. In some small cancers at the pylorus which cause early obstruction the obstruction may be marked and the deformity slight.

The malignant degeneration of an old ulcer may present great difficulty in diagnosis. Slight or marked irregularity in outline favors cancer, but is not distinctive. To put this more in detail, we may say that the chronic ulcer is often definite, the transition stage from ulcer to cancer usually indefinite and impossible to diagnose, the later cancerous stage usually definite and characteristic.

At the cardia the character of the shadow frequently does not distinguish cancer from other causes of obstruction. We may say in general that the technical evidence of cancer is *absolutely characteristic* in only part of the cases. In the majority, it must be judged in connection with other clinical data.

Early Cancer. The word "early" in this connection must include very small cancers. It is practically impossible to tell the "age" of many cancers of the stomach.

For early diagnosis of cancer we must see the patient early.

What brings the patient for examination? His symptoms. We shall not see him until he develops some. These early symptoms and signs of cancer are often vague. The important question is, Are the early anatomical changes in gastric cancer discoverable by *x*-rays more definite and characteristic?

We have tried to avoid delay in examinations and have used the *x*-rays in all suspicious cases in hopes of discovering the anatomical signs of early cancer.

This faithful search for early cancer in a large number of suspected

cases has given little result. The earlier the cancer the less clear the picture with the *x*-rays as with other methods until a point is reached where the evidence is very doubtful indeed. In primary cancer the small area of induration in the earliest cases may be in no wise characteristic; and in cancer developing on ulcer the transition stage may be very difficult or impossible to diagnose by the *x*-rays.

In short, while anatomical changes in the stomach wall, discoverable by the *x*-rays, accompany the early clinical symptoms, the anatomical changes themselves are not always definite and characteristic of cancer.

We have, however, one proved case with a possible second (both examined by Dr. A. W. George). A man, aged fifty years, had mild attacks of epigastric distress and vomiting for several years. Physical examination was practically negative. Gastric secretion was normal. No blood was found in gastric contents or feces. There was slight twelve-hour gastric stasis. A diagnosis of doubtful chronic ulcer was made. A diagnosis of cancer was made after *x*-ray examination on the basis of a very small annular defect at the pylorus, showing slight but definite irregularity, and resection urged. The surgical diagnosis at operation was chronic inflammatory tissue, but resection was done. The pathologist's report on gross examination was the same, but cancer was found on microscopic examination. We must give the radiologist the credit of making the correct diagnosis, and if such results are confirmed by a later series of cases they will prove of great value. We do not feel sure, however, that such *x*-ray evidence will always distinguish cancer from ulcer.

The second case, aged fifty years, had, several years before, severe distress and vomiting of several months' duration, some mild but continuous symptoms since. Physical examination showed nothing abnormal. There was normal gastric secretion, no stasis, and no evidence of bleeding. A diagnosis of very questionable old ulcer was made.

X-ray examination showed a slight defect at the pylorus, very slightly irregular, normal motility. A diagnosis of probable early cancer was made. At operation a slight induration was felt at

the pylorus, but the surgeon did not feel justified in operating upon the stomach. It is possible that in this case also the *x*-rays may precede the surgical diagnosis of cancer. It is also possible that the diagnosis after the *x*-rays is an error. Time will tell. Such early diagnosis, if experience justifies it, is brilliant and important. Further data are needed before passing an opinion.

One more case should be mentioned in this connection. A man, aged fifty-four years, with short history of distress and vomiting and loss of weight, showing poor gastric secretion, some stasis, and occult blood in the feces; in short, a "well-developed" case clinically was shown by *x*-ray examination to be relatively "early," to have a stomach wall almost entirely intact and a very small cancer at the pylorus, and proved an ideal case for operation. The *x*-ray examination did valuable service in urging the operation.

We may briefly summarize our experience in searching for early cancer as follows:

One of the greatest difficulties has been in getting the patient early. The first examination when positive has usually discovered well-developed, not early, cancer. Our *x*-ray evidence of early cancer is very scanty, but we believe the method will occasionally aid in its discovery, and should be given a trial in every suspected case. The better the *x*-ray technique and the more thoroughly the case is studied the better the chance for an early diagnosis. Well-marked cancers are easily found with fluoroscopic examination and a few routine plates. This is not true of early cases.

Dr. Cole[1] has recently stated that gastric cancer at any stage of development may be detected with as great a degree of accuracy as bone fractures. We cannot believe this is true, regardless of the number of plates taken. Neither do we believe that at present a positive or negative diagnosis after *x*-ray examination is as accurate in early cancer as an exploratory laparotomy or can replace it. On the other hand, patients of cancer age with few symptoms will consent to an *x*-ray examination readily when they would refuse an exploration.

[1] L. G. Cole, The Positive and Negative Diagnosis of Gastric Cancer by Means of Serial Rœntgenography, New York Med. Jour., February 14, 1914.

The *x*-rays will occasionally show in an evident case, with definite symptoms and signs, that the cancer is small and mobile and ideal for operation. This is almost as important as early diagnosis.

Latent Cancer. Cancer of the stomach may remain latent or hidden because no careful search is made for it. It is quite common nowadays for the radiologists to discover a large cancer in a stomach which has never been examined before by any method. These are not latent in a strict sense; they are found when looked for. On the other hand, there is a small group of cases which remain hidden or very doubtful after thorough clinical examination. These are latent in the strict sense in which we use the word in this paper.

We have been impressed with the size and extent of some of these latent cancers in comparison with the vagueness of gastric symptoms, the prompt emptying of the stomach, and sometimes the lack of significant bleeding, and also the ease with which they were discovered by the *x*-rays.

In our six latent cases the diagnosis was verified by operation. The patients were all of middle age or beyond; the symptoms were either vague and apparently due to age, arteriosclerosis, or syphilis, or pointed to the bowel or gall-bladder, when actually the stomach was involved. In other cases the diagnosis of ulcer was made and in others gastric catarrh or achylia. Prompt emptying of the stomach was the rule. The gastric secretion was either within normal limits, or if low, was attributed to functional disturbance, age or catarrh. Blood was either absent (in one or two cases) or not considered significant of cancer, being laid to slight abrasion of the stomach by the tube, to piles, ulcer, syphilis, etc. No tumor was felt.

We will consider the types of latent cancer of the stomach more in detail.

Case Called Senile or Functional. We have one example of this class where the vague symptoms and loss of weight seem to be well explained by the process of growing old, and the absence of gastric stasis (where the pylorus is not involved), and the lack of significant bleeding wake little suspicion of cancer. Low gastric secretion is considered functional and due to increasing age. The presence of some other lesion like interstitial change in the kidney is doubly

misleading and seems to account for the symptoms. The cancer was readily discovered and located with the aid of the *x*-rays on the lesser curvature, not obstructing the pylorus.

Case Called Catarrh of the Stomach. When chronic gastric catarrh is present, even though the patient is carefully studied and followed for years, the final development of cancer may come so quietly as to escape observation. The gastric secretion has long been so low that cancer does not lower it. There may be no twelve-hour stasis. The blood test may not be significant. In this case the passage of a stomach-tube had often provoked a tiny streak of blood and the patient had piles.

Case Called Syphilis. The presence of syphilis shown by skin or bone changes, and a strong Wassermann reaction may seem to explain all symptoms of a general kind, loss of appetite and moderate loss of weight, dull pains and distress, and even gastro-intestinal symptoms. Even the presence of blood in feces or gastric contents may be explained by syphilitic ulceration of the gastro-intestinal tract, and thus the evidences of cancer may be confused and overshadowed by the presence of the serious disease, syphilis, which is recognized.

The *x*-ray evidence in this case was definite and clear, but sometimes it is not. Syphilis sometimes resembles cancer too closely to be distinguished.

After *x*-ray examination we have two such syphilitic patients, both of cancer age, classed among the "doubtful cases." (One proved to have cancer also, the other was diagnosed as syphilis at operation, and subsequent history for a year confirms it.)

Cases Called Ulcer. Patients with a history of chronic recurrent ulcer, extending perhaps over many years, may readily develop cancer without important symptoms which call attention to the change. The weakness, pain, loss of weight, vomiting, or blood may all be laid to ulcer. Full or high gastric secretion helps to conceal the cancer. The bismuth defects in these cases were irregular, bitten out, and typical of cancer, and in one case surprisingly large.

The *x*-rays usually help the diagnosis between cancer and ulcer and will clearly distinguish advanced cases. In a large number

of the cancer cases, however, it will not differentiate between old ulcer and the malignant degeneration of old ulcer (see Doubtful Cases). Cole[1] in a recent paper makes no attempt to distinguish by the *x*-rays between chronic ulcer and cancer, and groups them together as "surgical cases."

Case Called Cancer of Other Organs. The patient's symptoms may point strongly to the bowel, or gall-bladder or other abdominal organ, and if at the same time the gastric functions are well preserved, even an advanced cancer of the stomach may be overlooked and a diagnosis made of cancer of the bowel or gall-bladder. This is far less serious than overlooking cancer altogether, for such cases are likely to be explored, but the vagueness of the clinical diagnosis contrasted sharply with the definite diagnosis of cancer of the stomach made at once after *x*-ray examination.

In looking over these latent cases it is important to note the position of the cancer. Most have been in the median part of the stomach, where they are hard to recognize clinically. No tumor is felt because the cancer is behind the ribs; the wide lumen is not obstructed. We have found that in most cancers in this region, even the large ones, the stomach empties more rapidly than normal.

The *x*-ray evidence has not only helped in discovering these latent cancers, it has also located them definitely and has shown their size and extent. It has given valuable evidence about operability in many cases (though we should often hesitate to decide this question on *x*-ray evidence alone). On the other hand the value of the diagnosis to the patient is limited by the fact that almost all the latent cancers discovered were large and inoperable.

We have discovered no latent cancers of the cardia in this series. The diagnosis has either been clear before *x*-ray examination or else has been doubtful after it. The early diagnosis of cancer of the cardia has less value at present than in cancer lower down, owing to the great difficulties of radical operation on the cardia.

Suspicious Cases. *X*-ray evidence has proved very valuable in ruling out cancer in a long list of suspicious cases, 63 in number. These include people of cancer age with various combinations of one

[1] Loc. cit.

or more suspicious symptoms, such as loss of weight and strength, anemia, epigastric pain or distress, vomiting, blood in vomitus or feces, epigastric tumor, poor gastric secretion, gastric stasis, and in which the final diagnoses were as follows: senility, arteriosclerosis, gastric neuroses, achylia, gastric catarrh, pernicious anemia, cirrhosis of the liver, cyst of the liver, gastric ulcer, syphilis, tumor of kidney, and other abdominal tumors, cardiospasm, chronic appendix, intestinal stasis, adhesions of gall-bladder to pylorus, tabes. Most of these patients were faithfully followed to operation or autopsy or for six or more months after examination to verify the diagnosis as far as possible. This has been our hardest task, but the results have been striking. Up to this time in no case in this group where a normal picture of the stomach was found has cancer been proved.

We have discovered very few early cases, and yet the method proved a great help in ruling out cancer. How explain this paradox? How can we rule out early cancer if we are not sure of detecting it? We believe the explanation is that the majority of patients did not come for examination in the very early or "incubation" period of cancer. Either a fairly developed cancer was present and readily found, or the symptoms were not due to cancer, and it was easily ruled out. When patients who have had symptoms a long time come for examination and we find a normal picture of the stomach, we can definitely rule out cancer as the source of symptoms and free the patient from uneasiness and constant observation.

Doubtful Cases. The following cases illustrate the limitations in *x*-ray evidence:

In a moderate number of cases (12) the diagnosis remained doubtful after all examination. These were mostly elderly people, all but 2 were aged fifty-five to sixty-eight years. In order of their frequency they were classed as follows: 6 ulcer or cancer; 2 syphilis of stomach or cancer; 2 organic stricture of cardia, nature not determined, probably cancer in one at least; 1 doubtful early cancer of stomach already referred to; 1 adhesions or cancer. All these cases had some defect or deformity of the stomach, 3 large, 5 moderate, and 4 small. Obstruction of the cardia was present in 2 cases and obstruction of the pylorus was moderate in

8, slight in 2, absent in 6. An absolute diagnosis between indurated ulcer and malignant degeneration of old ulcer is quite often impossible. Half the doubtful cases were of this type. Gastric secretion was practically normal; food stasis and blood were present.

Cases of syphilis sometimes resemble cancer too closely to be distinguished. Our 2 patients had triple positive Wassermann reactions and good-sized, irregular tumors in the median part of the stomach. Gastric secretion was very low and no stasis occurred. One at operation was considered syphilis of the stomach, the other cancer.

Cancer of the cardia is difficult in many cases to positively diagnose or rule out. The cardia is less accessible than the pylorus, cannot be manipulated, changes in peristalsis noted, etc., and the contour of the lesion is less clear than at the pylorus. Our two strictures proved to be one cancer, one benign.

In one man, aged fifty-five years, it was impossible from history examination, or *x*-ray to decide between gall-bladder adhesions and early cancer. There was previous history of colic and jaundice, the gastric secretions were a little below normal, there was slight gastric stasis and no blood in gastric contents or feces. A small defect was found, involving pylorus and duodenum. Operation refused.

The doubtful early case of cancer has already been discussed.

Mistakes. The following four cases illustrate errors in *x*-rays and other evidence. The diagnosis made before *x*-ray examination was cancer in three cases (two of stomach, one of gall-bladder), and in one chronic duodenal ulcer. The chief mistake lay in our anxiety to make as early a diagnosis of cancer as possible. Three of the patients were elderly, aged fifty-one to fifty-seven years; their symptoms and loss of weight were marked. Secretion was lowered in 2; blood was found in feces and gastric contents in 1. There was no gastric stasis. In short, we suspected cancer and overstepped the mark in our anxiety to make an early diagnosis.

In 3 cases after *x*-ray examination slight defects and irregularities in outline were interpreted as early cancer, 2 primary, 1 on an ulcer base, while in all 3 cancer was definitely ruled out, in 2 by operation

(finding one ulcer and one stomach with a few adhesions, evidently due to a healed ulcer) and in the third case, in which operation was refused, by practically complete recovery and good health ten months later. In the fourth case the error in diagnosis after *x*-ray examination was less important, but less easily explained. It consisted in diagnosing a tumor, external to the stomach, adherent, and indenting and deforming it, when it actually was a cancer of the stomach itself. The patient was a man, aged thirty years, with pain and "constriction" in the epigastrium for a year, vomiting, no blood seen, loss of fifteen pounds. There was slight twelve-hour stasis and high normal secretion. Blood was found intermittently in the stomach contents. An indefinite mass was occasionally felt in the epigastrium. The clinical diagnosis was cancer of the stomach. The *x*-ray examination showed hour-glass deformity, and a diagnosis was made of tumor in the region of spleen, deforming the stomach by indentation and spasm. The man's age and full gastric secretion may have biassed the radiologist in his diagnosis. Exploration showed an inoperable irregular tumor, the size of a base-ball, in the middle of the greater curvature, adherent posteriorly and extending as far as the spleen.

We have not thus far found a single case in our series in which cancer has been proved after being ruled out by our clinical and *x*-ray examination.

Our errors have been of commission not omission. The cases diagnosed cancer, which were not cancer, were partly the result of a desire to make a definite diagnosis in as many cases as possible. The moral is to recognize the limitations of *x*-ray evidence. This is the only way to avoid mistakes; in some cases the diagnosis must be left doubtful.

The mistakes we have been able to find are few, some may have escaped us in spite of careful search

Dr. Richard C. Cabot[1] in a recent paper found 72 per cent. of correct diagnoses in a series of cases of gastric cancer studied at the Massachusetts General Hospital. These cases dated back nearly twenty years. During that time the clinical study of the stomach

[1] Common Diagnostic Errors, Jour. Med. Soc. of New Jersey, 1912.

has become more complete and accurate. Functions are carefully tested and occult blood regularly looked for. It is interesting to compare with these older figures the correct diagnosis made in 34 operated cases in our series: before *x*-ray examination 83 per cent., after *x*-ray examination 89 per cent. (The balance of 17 per cent. and 12 per cent. respectively, represent cases remaining doubtful after all examinations and errors in diagnosis.) Modern clinical methods have helped much, and now the *x*-rays take us another step forward to better diagnosis of gastric cancer.

Summary. In the large majority of cases of cancer of the stomach at the time when they have presented themselves for our examination and if the stomach is thoroughly examined for secretion, motility, and bleeding by the usual clinical tests, the *x*-ray evidence has merely confirmed the diagnosis already made. These more or less typical cases we shall pass over as they are outside the scope of this paper.

Our *x*-ray evidence of early cancer of the stomach is very scanty, anatomical changes in the wall appear at the time of the early symptoms, but the early anatomical changes are hard to recognize; the earlier the cancer the less clear the evidence.

The small areas of induration in early primary cases are often not characteristic and the transition stage in cancer developing on ulcer is very difficult or impossible to distinguish from ulcer. The difficulties may be realized when we say that we have been more often wrong than right in our efforts to diagnose early cancer with the help of the *x*-rays.

Very rarely (in one or possibly two cases) in this series an early diagnosis has been made. We believe the very small number of these cases is due in part to the limitations of the method, and in part to the lack of sufficiently early examination.

The most important technical evidence is an irregular defect, with rigid stomach wall. The better the technique, the better the chance for early diagnosis. A few routine plates and fluoroscope examinations may not be enough. It has recently been said that by using a large number of plates, gastric cancer at any stage of development may be as accurately detected as a bone fracture, and also that *x*-ray diagnosis whether positive or negative is as

accurate in gastric cancer as a laparotomy. We do not agree to either statement.

Early examination is necessary for early diagnosis. In order to find early cancer, patients must be examined more early and often than is now the rule. The ideal seems to be early examination of every patient of cancer age who has digestive disturbance.

While our *x*-ray evidence of early cancer is very scanty, we believe the method will occasionally aid in its detection, and should be given a trial in every suspected case.

It is well recognized that a small group of cancers, probably not over 10 per cent., remain latent even when well developed. This group increases in size if the patients are carelessly examined, and shrinks if modern clinical methods are faithfully used. In this small group of latent cases *x*-ray evidence has been valuable in making a clear, definite diagnosis when other signs were doubtful. This has most frequently occurred with cancers in the median part of the stomach, in which the stomach emptied rapidly. The most common latent cases were cancers developing on old ulcer, or anacid cases called senile, catarrh or achylia, or patients with syphilis. We must admit that the value of the diagnosis to the patients was limited by the fact that all our latent cases were well developed when discovered, and resection was only possible in one instance.

X-ray evidence has been valuable in helping to rule out cancer in a long list of suspicious cases. In no case where a normal picture of the stomach was found has cancer been proved to exist. In our whole group of cases we may say that either no cancer or well-developed cancer was usually found. We believe this occurred because most cases did not come for examination in the "incubation" period.

X-ray evidence has its limitations. After all examinations a doubtful group remained about twice as large as the group of latent cases discovered. These were cases of disease at the cardia or where the diagnosis lay between cancer and ulcer or syphilis.

A few mistakes were made in our anxiety to make an early diagnosis in suspicious cases; we overstepped the mark three times and diagnosed cancer where it was absent. We must recognize

the limitations of the method and occasionally leave the diagnosis doubtful and have the patient explored.

In spite of these limitations and errors the *x*-ray evidence had distinctly improved our diagnosis. In 34 operated cases the correct diagnosis before *x*-ray examination was 83 per cent., after *x*-ray 89 per cent. It is almost needless to say that we have studied the *x*-ray findings in connection with the other clinical data and have not attempted to build a diagnosis on *x*-ray data alone. This addition of the *x*-ray method to our other examinations gives an accuracy and completeness to our diagnosis impossible with either alone.

In addition to aiding in diagnosis the *x*-ray evidence has definitely located the cancer, shown its size and extent, and helped decide about operability. It may show that a cancer with marked symptoms is small and mobile and ideal for operation.

In short the *x*-ray evidence has been a help in discovering and localizing latent cancer and an equal help in ruling out cancer. Our known mistakes have been few, and the group of doubtful cases rather small, and it seems reasonable to expect that with better technique and greater experience, less mistakes will occur and less cases remain doubtful, and with more early and frequent *x*-ray examination of patients of cancer age that early diagnosis will be more frequently made, and latent cases discovered earlier, so that radical operation will be possible.

THE CLINICAL VALUE OF EXPECTORANTS

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An accurate bedside study of the action of expectorants offers at present apparent insurmountable difficulties. Patients with acute bronchial troubles are unsuited for study on account of the rapid and marked spontaneous changes that may occur. Those with chronic bronchitis, where the daily or even weekly variations are imperceptible, are most suited for a study of this character. In these patients, however, it is apparently impossible to determine accurately the amount and viscosity of the sputum. The admixture of saliva and the length of time the secretion has remained in the trachea or bronchi with consequent loss of water must all be considered. These difficulties probably account for the absence in the literature of any accurate bedside observations.

The review of the literature is comparatively simple, as the total published information upon this subject, outside of that contained in the text-books on pharmacology, is confined to less than a half-dozen monographs. The total evidence at hand, therefore, consists of purely theoretical consideration and three or four series of observations performed upon laboratory animals, to which we have added some additional laboratory experiments.

Expectorants may be defined as agents which facilitate the removal of secretion from the air passages. Several factors play a role in this process. The act of coughing, by increasing air currents, carries upward the secretion in the trachea and large bronchial tubes, but has no effect upon the bronchioles. In these latter the chief factor is the ciliary movements of the bronchial mucosa. It has been determined by Gebhart, Henderson and Taylor, and others that the ciliary activity is capable of carrying

mucus 1.5 to 2.5 cm. per minute. Increased viscosity of the mucus interferes materially with this movement, and Engelmann has shown that it may entirely inhibit the action of the cilia. The third factor is the presence in the alveoli and smaller bronchiole of a peristaltic-like movement; this is probably under vagus control (Einthoven, Sandimann). These movements somewhat resembling intestinal peristalsis, are probably important factors in removing the mucus from the alveoli and terminal bronchioles, neither of which are provided with cilia. To facilitate removal of mucus it would, therefore, be necessary to stimulate coughing, increase the ciliary movements, lessen the viscosity of the secretion, or stimulate bronchial peristalsis.

The cilia are not supplied with nerves, and it is therefore impossible to stimulate them through the nervous system. Virchow, in 1854, demonstrated that the direct application of weak alkalies increased the activity of the cilia, and Rossbach claimed that alkalies by mouth had the same effect. Cushny states that alkalies are not secreted through the bronchial mucosa, and certainly in the ordinary doses the amount so secreted must be negligible. It is, therefore, highly improbable that any of the expectorants increase the ciliary movement.

There is no evidence that any of the expectorants increase the rhythmical muscular contraction in the bronchioles. It is possible that apomorphin in large doses may stimulate the vagus and thus increase peristalsis.

The final possibility is the action of expectorants in thinning the bronchial secretion. The trachea and bronchi are richly supplied with mucous glands capable of producing a profuse secretion. The viscosity of this secretion may be lessened either by increasing the amount of secretion or by introducing into the secretion something which would dissolve the mucus, as for instance an alkali.

The expectorant action of ammonium chloride and ammonium carbonate was thought to be due to their eliminatiom through the bronchial mucosa, the alkali thinning the secretion. This theory, however, will not bear close scrutiny. Biedl, Winterberg, and others have shown that one-half to four-fifths of the ammonia administered disappears in the liver, never reaching the systemic

circulation. In the ordinary therapeutic dose of 0.3 gm. not more than 0.15 gm., or 2.5 grains, would reach the general circulation, and at most only a small part of this would be excreted by the bronchial mucosa, an amount certainly too small to modify the viscosity of the mucus. In case, therefore, the ammonium salts mentioned thin the mucous secretion they must act through some different channel. It is now believed that their action is upon the bronchial gland centre, which, in its activity, apparently shows a parallelism with the salivary centre. It is thought that the centre may be stimulated directly by substances in the blood or reflexly, especially from the stomach and mouth. Biedl and Winterberg have shown that in order to stimulate this centre in dogs it requires 2 to 2.5 mg. of ammonium salts per 100 gm. of blood. They found that when injected intravenously into a 7-kilo dog 0.48 gm. of ammonium chloride was required, and if given by the mouth twice this amount, equivalent to about 9 gm. in a man.

Turning to a consideration of the experimental work performed with ammonium salts, Rossbach, in 1882, endeavored to determine the amount of tracheal secretion in cats by exposing the interior of the trachea by means of a longitudinal slit and then observing the secretion directly. The exposed mucosa was dried with filter paper and the time noted in which secretion occurred. Drugs were then given and the secreting time again observed. He used very large doses of ammonium carbonate, 2 gm. intravenously, and reported a definite delay in the secretion time. He also failed to increase secretion by painting the mucosa with a 1 per cent. solution of ammonium carbonate.

Calvert, in 1896, repeated Rossbach's experiments with quite different results. He refers to only two experiments, both on cats. He reports that after the intravenous injection of 2 gm. of sodium carbonate there was a shortening of the secretory time of one minute. Considering the method employed, namely, the covering of a previously dried surface with a secretion, this difference in time is too slight to enable us to draw any conclusions. Henderson and Taylor call attention to the late appearance of the secretion in one of Calvert's cases, thirty-seven minutes, as after an intravenous injection the effect should be noted within ten or twenty minutes.

The possibility of such a surface being moistened by secretion carried up from below by the cilia makes another probable source of error.

Henderson and Taylor, in 1910, studied the action of expectorants by the following method: Cats were anesthetized with chloroform or ether, or both. This was followed by urethane, which kept the animal asleep during the period of observation. One limb of a Y-tube was fastened into the trachea, another to a calcium U-tube and the other limb to the blast side of a Meyer respiratory pump, the exhaust end of which was attached to the other end of the calcium U-tube. The animal was placed upon its belly on an incline to assist in the escape of mucus. By this method not only the mucus but the water also contained in the expired air was estimated. This latter factor apparently introduces an element of error, as they found it varied with the temperature of the animal, the amount of air forced into the lung, and the state of the animal's circulation. They reported that ammonium carbonate or ammonium chloride in large doses given intravenously equivalent to 12 gm. for a 70-kilo man, caused marked increased secretion of mucus. Two and a half times this dose, an equivalent of 30 gm. for a man, given by mouth, also caused increased secretion. Doses of 40 mg. of ammonium carbonate intravenously, equivalent to 1 gm. in man, at times failed to produce any increased secretion. In one instance 50 mg. of ammonium chloride intravenously, equivalent to 1.25 gm. in man, failed to inrease secretion. The dosage with which they obtained results was far in excess of that usually employed by the clinician, and therefore it may be said that they have not shown that in man these drugs in the ordinary therapeutic dose acts as expectorants. When they obtained results an increased secretion appeared in about ten minutes and was transitory in character, rarely lasting more than twenty minutes.

On account of the conflicting reports upon the action of the ammonium salts on bronchial secretion the following experimental work was carried out. Oblong pieces of filter paper of uniform weight and size, 6 x 12 cm., were rolled in such a manner so as to fit into the trachea and still leave a lumen of about 1 cm. Dogs averaging about 7 kilos were anesthetized by giving 5 gm. of chlore-

tone in alcohol. The trachea was then severed transversely, just below the larynx, all bleeding stopped by means of the cautery, and a weighed rolled filter paper introduced. This came in close contact with the mucosa for a distance of about 6 cm. Such a filter was left in place ten minutes, then reweighed, and the increase taken as an index of the amount of secretion from the mucosa. This should also include some of the moisture in the expired air and mucus carried up from below. After two control readings of ten minutes each the ammonium carbonate in moderate doses was injected directly into the duodenum, and then another series of readings were taken, each of ten minutes, and continued for thirty minutes or more. Four animals in all were used.

The following results were obtained with ammonium carbonate:

Dog I, 7.2 kilos, received 5 gm. chloretone in 50 per cent. alcohol. Increase in weight of filter paper during the two control periods was 0.2 and 0.12 gm. The increase in weight after 0.3 gm. of ammonium carbonate for three periods of ten minutes each was 0.18, 0.14, 0.16 gm. respectively.

Dog II, 6.5 kilos, received 5 gm. chloretone in 50 per cent. alcohol. Increase in weight of filter paper during the two control periods 0.9 and 0.4 gm. respectively. The increase in weight after 0.25 gm. of ammonium carbonate for three ten-minute periods was 0.4, 0.4, and 0.4 gm. respectively.

Dog III, 7 kilos, received 5 gm. chloretone in 50 per cent. alcohol. Increase in weight of filter paper during the two control readings 0.19 and 0.17 gm. respectively. The increase in weight after 0.5 gm. of ammonium carbonate for three periods was 0.17, 0.16, and 0.17 gm. respectively.

Dog IV, 7.5 kilos, received 5 gm. of chloretone in 50 per cent. alcohol. Increase in weight of filter paper during the two control periods was 0.2 and 0.14 gm. respectively. The increase in weight after 0.25 gm. of ammonium carbonate for three ten-minute periods was 0.14, 0.12, and 0.12 gm. respectively.

These experiments show that at least by the method pursued ammonium carbonate, in what would be called moderate laboratory doses for a dog, does not increase bronchial secretion. The dosage varied from 0.25 to 0.5 gm., equivalent to 2 to 4 gm. for a 65-kilo

man, an amount considerably in excess of the ordinary therapeutic dose.

Both experimental and clinical evidence would indicate that the iodides cause increased secretion of bronchial mucus. Henderson and Taylor, from their experimental report, believe that this must be due to reflex stimulation of the bronchial centre from the stomach, as in their experiments iodides used intravenously did not modify the bronchial secretion. The iodides, as shown by Baehr and Pick and others, also cause dilatation of the bronchioles. It is possible this may play some role in facilitating the removal of mucus.

Many of the drugs having an emetic action also act as expectorants. Attention has already been called to the apparent intimate relation between the salivary and bronchial gland centre. The most important members of this group are apomorphin and ipecac. Both of these in non-emetic doses are supposed to cause increased bronchial secretion. Apomorphin probably acts chiefly by direct stimulation of the bronchial gland centre; ipecac both centrally and reflexly from the stomach. These drugs when pushed to the point where they have an emetic action may possibly through their vagus action also cause increased peristalsis of the smaller bronchioles. Senega, according to Henderson and Taylor, probably acts as an expectorant by affecting the bronchial gland centre reflexly from the stomach. Pilocarpin stimulates the bronchial glands directly.

Rossbach, Calvert, and Henderson and Taylor agree that ipecac and apomorphin act as expectorants in animals. Calvert failed to obtain results with senega, but Henderson and Taylor produced marked increased bronchial secretion in cats. Henderson and Taylor also obtained positive results with antimony and tincture of squill. The uniformity of these results leaves no doubt that in the doses used these drugs act as expectorants on dogs and cats. Henderson and Taylor call attention to one point, namely, that the bronchial-gland centre is easily depressed and then fails to act. Especially with apomorphin a slight excess in dosage by depressing this centre would lessen bronchial secretion. They raise the question as to whether in diseased conditions with marked circulatory disturbance the bronchial-gland centre would react as in the normal.

The dosage employed in all this experimental work was quite large. Henderson and Taylor gave 1 c.c. of the fluidextract of ipecac intravenously and 2 c.c. of the wine of ipecac by mouth to a $2\frac{1}{4}$-kilo cat. This would be equivalent to 25 and 50 c.c. in man. This dose is, of course, far in excess of that employed clinically. Their results with senega and squill were obtained by using 2 c.c. of the tincture of each in a $2\frac{1}{2}$-kilo cat: here, again, doses far in excess of that employed in man. They have not, therefore, proved that any of these drugs are active in the ordinary therapeutic doses, which after all, from a clinical stand-point, is most important. For this reason we thought it desirable to repeat these experiments, using moderate doses.

The expectorant action of ipecac and apomorphin was tested on four dogs. The method of procedure differed very slightly from that used in the experiments with ammonium carbonate. After severing the trachea the roll of filter paper was introduced into the upper portion rather than the lower, as in the previous experiments. This method offers two advantages: (1) that absorption of moisture from the expired air is avoided, and (2) only mucus from the surface in contact with the filter paper is obtained, as in the previous method much mucus may be carried upward by ciliary action.

Chloretone was employed as an anesthetic in three of the animals, urethane in one. The emetin was injected directly into the stomach, the apomorphin into the duodenum. In each instance the filter paper was allowed to remain in contact with the mucosa ten minutes. Two control readings were taken before administering the drug. Readings were taken for at least forty minutes after giving the drug, which should be sufficient time to permit of a physiological action occurring.

The following results were obtained with emetin hydrochloride:

Dog V, 7.8 kilos, received 5 gm. of urethane and 2 gm. of chloretone in 20 c.c. of 50 per cent. alcohol. Increase in weight of filter paper during the two control periods was 0.65 and 0.69 gm. respectively. The increase in weight after 4 mg. of emetin hydrochloride for three periods of ten minutes each was 0.262, 0.0525, and 0.0495 gm. respectively.

Dog VI, 6.7 kilos, received 5 gm. of chloretone in 20 c.c. of 50 per cent. alcohol. Increase in weight of filter paper during the two control periods was 0.0613 and 0.062 gm. respectively. The increase in weight after 4 mg. of emetin hydrochloride, for three periods of ten minutes each, was 0.058, 0.056, and 0.05 gm. respectively.

The following results were obtained with apomorphin sulphate:

Dog VII, 9 kilos, received 2.5 gm. of chloretone, in 15 c.c. of 50 per cent. alcohol. Increase in weight of filter paper during two control periods was 0.08 and 0.0746 gm. respectively. The increase in weight after 2 mg. of apomorphin for three periods of ten minutes each was 0.0727, 0.0664, and 0.0643 gm.

Dog IX, 8 kilos, received 5 gm. of chloretone in 20 c.c. of 50 per cent. alcohol. Increase in weight of filter paper during the two control periods was 0.06 and 0.055 gm. respectively. The increase in weight after 2 mg. of apomorphin sulphate was 0.054, 0.058, and 0.055 gm. respectively.

It will be noticed that the first reading in each instance was considerably higher than the subsequent ones. This can probably be accounted for by mucus which had collected in the trachea, and, therefore, does not represent the real secretion during the period. At the beginning of the experiment there was frequently slight bleeding from the severed end of the trachea; this added to the weight of the filter paper.

The apparently much greater secretion of mucus in Dogs I to V in both controls and after receiving the drug was due to the roll of filter paper being introduced in the lower segment of the severed trachea, so that much of the mucus on the filter paper was carried up by the cilia from below and also from moisture in the expired air. The filter paper was introduced into the upper end of the trachea in Dogs VI to IX, the increase in weight here probably being due almost entirely to mucus secreted from the surface covered by the filter paper.

I wish to express my appreciation of the valuable suggestions and assistance rendered by Prof. A. P. Matthews, of the University of Chicago.

SUMMARY.—Ammonium carbonate and ammonium chloride and the emetic group of expectorants, as apomorphin and ipecac, when given in sufficiently large doses to animals, increase bronchial secretion. Ammonia salts by mouth, in moderate doses equivalent to 2 gm. in an adult man, do not increase bronchial secretion in the dog. Apomorphin and emetin when given to dogs in doses considerably greater than the ordinary therapeutic dose for man do not excite increased bronchial secretion.

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DISCUSSION

DR. S. J. MELTZER: I well remember the experiments of Rossbach; they were published in 1882. He studied the action of apomorphin and of ammonium chloride; but not of ammonium carbonate which should not be used as an expectorant; it is only a stimulant. Dr. Miller does not draw any conclusion from his experiments. I am inclined to disagree with him on some points. In the first place, I believe that careful records made at the bedside are as good as experiments on animals. The only objection which we generally have to bedside observations for the purpose of study is that they are not made as critically as experiments are or should be made. From the point of view of the bedside observation, there are three kinds of expectorants. As the first group of expectorants I shall mention the irritants; by producing irritation in the larynx, trachea or bronchi it leads indirectly to secretion of mucus. The second group consists of remedies which cause nausea when given in larger doses; in small doses they bring on secretion and expectoration; ipecac and apomorphin are representatives of this

group. The drugs of the third group bring on secretion directly. Ammonium chlorid in large doses is, I believe, a reliable remedy for increasing secretion and expectoration.

I have been dabbling in experimental work for thirty-five years; but I lay as much stress upon what I have seen at the bedside as I do upon any experiments I have made. I am quite certain that the remedies under discussion are useful and should not be discarded on account of the failure of some experiments on normal dogs to bear them out.

Dr. Henry Sewall: I would like to express the view that in Dr. Miller's experiments we have a most brilliant example of the value of the remarks made by Dr. Meltzer a little while ago as to the essential difference between the sick and well; that is to say, the state of receptivity of the vital cell determines its response to irritation. Our grandfathers in giving these expectorants carefully chose the period in which they gave them. They did not give them when the cells were not ready to work, but at a time when the secretion was prepared and hesitating to flow. It seems to me, therefore, that these experiments are valuable not because they disprove the value of expectorants, but because they show how important is the consideration of the vital phase of the reacting mechanism.

Dr. L. F. Barker: I agree with Dr. Meltzer that we have some strong clinical evidence that expectorants are effective in increasing the secretion of the bronchi and in liquefying it. Anyone who has tried to secure enough sputum for macroscopic examination in suspected pulmonary tuberculosis by administering potassium iodid or ammonium chlorid, knows that they are effective. I think, too, that there is no doubt that we can increase the secretion by irritating the stomach in a reflex way. The old senega preparations and scilla (Squill) act in this way. Apomorphin appears to act directly on the centres.

Dr. Abraham Jacobi: Just a word for the benefit of Dr. Miller. If he wants effects from an expectorant and does not believe in chlorid of ammonium, as I believe in it for the purpose of softening the secretion, in cases without temperatures, let his patients inhale the smoke of chlorid of ammonium. If he will be good enough to give 15 to 20 grains or more, by evaporation, filling the whole room, if necessary, with a white cloud, he will have an effort. In advanced cases of pneumonia or chronic bronchitis where expectoration is wanted, he may do the same thing either with camphor in good doses or with benzoic acid, which is very little used for that purpose, or by filling the air of a room with turpentine vapors.

Dr. Miller (closing): In my paper I stated the reasons why it was difficult to carry on bedside observations accurately.

A CLINICAL STUDY OF ONE THOUSAND CASES OF CANCER OF THE STOMACH

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In a study of one thousand cases of gastric cancer it was deemed advisable, so far as it was possible, to compare the character and frequency of the symptoms appearing in this disease with those observed in the cases of gastric ulcer presented to this Association[1] two years ago.

The 1000 cases of cancer occurred in 10,416 patients affected with various gastric disturbances (9.6 per cent.); this is in comparison to a similar number of cases of peptic ulcer appearing in 12,598 (7.8 per cent.) patients.

The maximum liability to the disease lies between the fortieth and sixtieth year (65 per cent.); the greatest number of cases occurring between the fiftieth and sixtieth years.

Age. In the following table the number of cases of cancer are presented according to age:

Years.	Cases.	Per cent.
20 to 30	4	0.4
30 to 40	37	3.7
40 to 50	261	26.1
50 to 60	395	39.5
60 to 70	218	21.8
70 to 80	85	8.5

This may be compared with the cases of gastric ulcer in which the largest proportion of cases occurred between the twentieth and fiftieth years as is presented in the accompanying table.

[1] Amer. Jour. Med. Sci., 1912, cliv, 157.

Sex. The greater proportion of cases occur in males; 588 males to 412 females. The following table illustrates the number of cases observed in males and females according to age:

Years.	Cases.	Per cent.
0 to 10	2	0.20
10 to 20	162	16.20
20 to 30	345	34.50
30 to 40	229	22.90
40 to 50	128	12.50
50 to 60	93	9.30
60 to 70	38	3.80
Over 70	3	0.30

Years.	Males.	Females.	Total.
20 to 30	3	1	4
30 to 40	23	14	37
40 to 50	125	136	261
50 to 60	249	146	395
60 to 70	143	75	218
70 to 80	45	40	85
	588	412	1,000

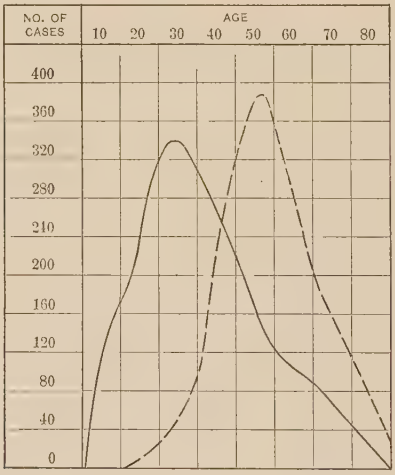

Fig. 1.—Age diagram of one thousand cases of ulcer and one thousand cases of cancer.

This is in comparison with the cases of ulcer in which there were 676 males and 324 females, divided according to age in the following table:

Years.	Males.	Females.	Total.
0 to 10	2	0	2
10 to 20	124	38	162
20 to 30	262	83	345
30 to 40	119	110	229
40 to 50	91	37	128
50 to 60	48	45	93
60 to 70	29	9	38
Over 70	1	2	3

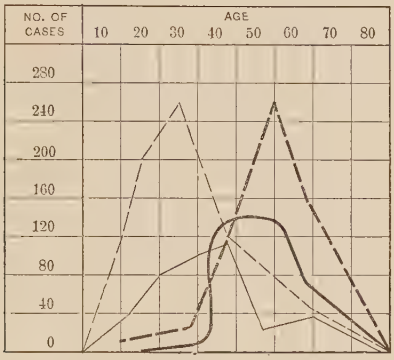

Fig. 2.—Sex and age diagram of one thousand cases of ulcer and one thousand cases of cancer. Dotted heavy black line, male cancer. Solid heavy black line, female cancer. Dotted light black line, male ulcer. Solid light black line, female ulcer.

Nationality. The following table indicates the relative proportion of cases among various nationalities, 75 per cent. being Americans:

Nationality.	Number.	Per cent.
American	753	75.3
German	123	12.3
Russian	96	9.6
English and Irish	17	1.7
South American	5	0.5
Other countries	6	0.6

Race. Of the 1000 cases there were 948 whites and 52 colored, that is, 94.8 per cent. whites and 5.2 per cent. colored.

The small proportion of colored persons noted is due to the fact that but a small number of colored patients come under our observations. The following table indicates the number of colored males and females classified according to age:

Age.	Males. Cases.	Per cent.	Females. Cases.	Per cent.	Total. Cases.	Per cent.
30 to 40	2	3.4	0	0	2	3.4
40 to 50	2	13.4	3	5.7	10	19.2
50 to 60	16	30.7	9	17.3	25	47.0
60 to 70	9	17.3	3	5.7	12	23.0
70 to 80	3	5.7	0	0	3	5.7
	37	70.5	15	28.7	52	

There were 37 males (70 per cent.) to 15 females (28 per cent.), the largest number occurring between the fiftieth and sixtieth years.

Heredity. An hereditary history of cancer appearing in various portions of the body occurred in 104 of the 1000 cases (10.4 per cent.). Of these there were:

	Cases.
With a family history of cancer of the stomach	22
" " " " " " uterus	37
" " " " " " breast	24
" " " " " " throat	5
" " " " " " rectum	11
" " " " " " face	5
	104

The following table indicates the ages of the cases presenting a family history of cancer showing that the largest proportion of cases occur in those years in which the greatest number of cases of cancer of the stomach occur:

Age.	Cases.	Cases with family history of cancer.
20 to 30	4	0
30 to 40	37	0
40 to 50	261	33
50 to 60	395	44
60 to 70	218	22
70 to 80	85	5
	1000	104

Trauma. A definite history of trauma was elicited in 19 cases, in 6 of which there had been blows on the abdomen.

Anemia. In 229 of our cases in which hemoglobin estimations had been recorded, anemia was present in 189 (82 per cent.). The average of the hemaglobin estimations was 43.

Cardiac and Vascular Changes. Chronic endocarditis was present in 114 cases (11.4 per cent.); arteriosclerosis in 696 (69.6 per cent.) of all cases.

As is observed in the following table the largest proportion of cases of cancer with arteriosclerosis occurred after the fiftieth year of life.

Age.	Cases.	Cases with arteriosclerosis.	Per cent. of cases with arteriosclerosis.
20 to 30	4	0	.0
30 to 40	37	0	.0
40 to 50	261	89	12.7
50 to 60	396	321	46.1
60 to 70	218	201	28.7
70 to 80	85	85	12.5

Blood-pressure. Of the 132 cases in which blood-pressure examinations were recorded, 121 (91 per cent.) present readings of 170 mm. or more. The following table presents this condition at various ages:

Age.	Cases with blood-pressure 170 to 180 mm.	Cases with blood-pressure, 180 to 190 mm.	Cases with blood-pressure 190 to 200 mm.	Cases with blood-pressure 200 to 210 mm.	Total.
40 to 50	2	5	4	1	12
50 to 60	21	12	13	8	54
60 to 70	7	22	6	3	38
70 to 80	1	7	4	5	17
Total	31	46	27	17	121

Renal Changes. Records of urinary examinations were recorded in 717 of the 1000 cases; albumin was present in 401 (55.9 per cent.), and albumin and casts in 334 (46.4 per cent.).

Previous Disorders of Digestion. In the 1000 cases of cancer there was a history of some previous digestive trouble in 232 cases (23.2 per cent.). Of the 232 cases, 109 had slight attacks of indigestion for a period of five years or more preceding the present gastric disease, while 25 had slight attacks only during the last five years preceding the present disease. Of the remaining 123 cases, 32 had chronic indigestion more or less all their lives, of which 29 had chronic indigestion, mainly during the last five years preceding the present illness. Seventy-three cases gave a definite history of former gastric ulcer. It is therefore evident that of these 1000 cases, but 23 per cent. presented a history of any previous digestive disturbance whatever, even in the slightest degree, and that but 7.3 per cent. give a direct history of ulcer. If, therefore, all of the former digestive disturbances be considered as due to ulcer the formation of gastric cancer from ulcer could not have taken place

in more than 23 per cent.; if all of these cases with slight digestive disturbances be disregarded in our series, this percentage is reduced even to 12.3 per cent.

Excesses in Food and Drink. A history of former indiscretions in diet was obtained in 321 instances (32.1 per cent.), and in but 137 (13.7 per cent.) did the patient attribute his disease to some specific error in diet. A history of alcoholism was obtained in 152 instances (15.2 per cent.).

Infectious Diseases. A history of syphilis was obtained in 79 instances; tuberculosis of the lungs was present in 48 instances.

The Gastric Secretion in Cancer. Of the 1000 cases the gastric secretion was examined in 733 instances:

	Cases.	Per cent.
Normal acidity was observed in	23	3.1
Hyperchlorhydria was observed in	35	4.1
Hypochlorhydria was observed in	21	2.8
Anacidity was observed in	654	89.2

Over 89 per cent. of our cases presented an entire absence of free hydrochloric acid. In comparison with the 810 cases of ulcer in which the gastric secretion was examined the result is as follows:

	Ulcer.		Cancer.	
	Cases.	Per cent.	Cases.	Per cent.
Normal acidity was observed in	376	46.4	23	3.1
Hyperchlorhydria was observed in	246	30.3	35	4.9
Hypochlorhydria and acidity in	188	23.2	675	92.0

Of the 733 cases, consisting of 443 males and 290 females, the acidities are as follows:

	Males.	Per cent.	Females.	Per cent.
Normal acidity	16	2.1	7	0.9
Hyperchlorhydria	17	2.3	18	2.5
Hypochlorhydria	13	1.7	8	1.1
Anacidity	397	54.1	257	35.2

Lactic Acid. Lactic acid was present in 601 instances, or 81.9 per cent. of the 733 cases in which the gastric secretion was examined. It was present only in any appreciable amount in those cases in which there was a complete absence of free hydrochloric acid.

Wolff-Junghans Test. The Wolff-Junghans test for dissolved albumin has been found exceedingly valuable in the diag-

nosis of gastric cancer but has not been employed sufficiently in this special series of cases to be incorporated in this report.

Oppler-Boas Bacilli. The Oppler-Boas bacilli were observed in 582 cases, or 79.3 per cent. of the 733 cases. They were found only in those instances in which lactic acid was observed.

Sarcinæ were observed in 24 instances (32 per cent.).

Visible blood were observed in the gastric contents in 129 instances (7.5 per cent.).

Coffee-ground contents was obtained in 653 instances (61.8 per cent.).

Röntgen-ray examinations were made in 32 instances, 8 cases presenting cancer at the cardiac region and 24 at the pyloric region. In those instances with cancer at the cardia a dilatation of the esophagus was revealed. In 5 of these cases the condition was confirmed by means of the esophagoscope. In the Röntgen-ray examination of the pyloric cases the characteristic sawed-off pylorus with retention was observed and frequently a filling defect.

Symptoms. *Onset.* Of the 1000 cases, 232 (23.2 per cent.) presented histories of some previous digestive disturbance, while 759 (75.9 per cent.) gave histories of sudden acute onset; attributing the origin of the disorder to some definite error in diet in 137 cases (13.7 per cent.). In the remaining 9 (0.9 per cent.) the character of the onset could not be determined. From the following table it is evident that proportionately the largest number of younger patients affected with cancer are found among those individuals who have had previous digestive disturbances; the reverse is true of those cases in which the disease comes on acutely without previous digestive upsets:

	Males.				Females.			
Years.	No.	Acute onset.	Previous digestive trouble.	Undetermined.	No.	Acute onset.	Previous digestive trouble.	Undetermined.
20 to 30	3	2	1	0	1	0	1	0
30 to 40	23	3	19	1	14	5	9	0
40 to 50	125	77	46	2	136	99	35	2
50 to 60	249	47	32	0	146	102	44	0
60 to 70	143	112	29	2	75	65	9	1
70 to 80	45	42	3	0	40	35	4	1
Total	588	453	130	5	412	306	102	4

Of the 73 cases that gave a distinct evidence of former gastric ulcer the largest proportion occurred in younger individuals, that

is before the fiftieth year of life; the large number occurred in males. The following table illustrates this condition:

Years.	Males. Total cases.	Males. Evidence of former gastric ulcer. No.	Males. Evidence of former gastric ulcer. Per cent.	Females. Total cases.	Females. Evidence of former gastric ulcer. No.	Females. Evidence of former gastric ulcer. Per cent.
20 to 30	3	0	.0	0	0	.0
30 to 40	23	12	16.4	14	6	8.2
40 to 50	125	19	26.0	136	15	20.5
50 to 60	249	11	15.0	146	6	8.2
60 to 70	143	3	4.1	75	1	1.3
70 to 80	45	0	.0	40	0	.0
	588	45	61.5	412	28	38.2

Duration of Life. The duration of life in cancer of the stomach varies greatly. In 472 of the 1000 cases (278 males and 194 females) by far the greatest number of deaths occurred between six and twelve months after symptoms were first observed both in males and females and the smallest number between twelve and eighteen months.

Years.	Total males.	Total number of cases in which duration of symptoms were noted.	Cases with duration of life up to 3 months.	Duration of life from 3 to 6 months.	Duration of life from 6 to 12 months.	Duration of life from 12 to 18 months.	Duration of life from 18 to 24 months.	Duration of life over 2 years.	Total females.	Cases in which duration of symptoms were noted.	Cases with duration of life up to 3 months.	Duration of life from 3 to 6 months.	Duration of life from 6 to 12 months.	Duration of life from 12 to 18 months.	Duration of life from 18 to 24 months.	Duration of life over 2 years.
20 to 30	3	3	0	0	1	2	0	0	1	1	0	0	1	0	0	0
30 to 40	23	15	4	2	2	0	5	2	14	11	5	2	2	1	1	0
40 to 50	125	53	9	15	12	1	9	7	136	67	6	11	19	2	18	11
50 to 60	249	108	19	24	32	1	12	20	146	46	5	18	8	3	10	2
60 to 70	143	72	16	8	24	8	10	6	75	50	11	2	26	3	6	2
70 to 80	45	27	5	9	0	5	6	2	40	19	8	2	8	0	1	0
Total	588	278	53	58	71	17	42	37	412	194	35	35	64	9	36	15

The above table illustrates this condition. From it is evident that of the 472 cases in which the duration of life was noted 316 cases (182 males and 134 females) died within one year

of the first appearance of symptoms of the disease, 104 (59 males and 45 females) died between one and two years and 52 (37 males and 15 females) died after two years.

Acute Cases. Of the 472 cases of the 1000 cases, 88 (53 males and 35 females), or 18.6 per cent., ran an acute course, that is, these patients died within three months after the appearance of the first symptoms.

Long Duration. *Chronic Course.* Of the 472 (37 males and 15 females), 11 per cent. ran a chronic course, that is, a course of over two years.

Periods of Improvement in Weight and General Conditions. Of the total number (472) in which duration of symptoms were noted, during almost the entire course of the disease, 145 (30.8 per cent.), 93 males and 52 females) presented periods of improvement in weight and general conditions.

Gain in Weight and General Improvement with Amelioration of Symptoms. Of the 145 cases presenting periods of improvement (93 males and 52 females) 26 males showed a gain in weight from five to thirty-five pounds, while the remaining 67 showed improvement in the general condition, with amelioration of symptoms; 11 females showed a gain in weight from five to twenty pounds while the remaining 41 showed improvement in the general condition with amelioration of symptoms. The following table illustrates this condition:

Males.

Years.	Cases with periods of improvement.	Gain of five pounds.	Gain of ten pounds.	Gain of fifteen pounds.	Gain of twenty pounds.	Gain of thirty pounds.	Gain of thirty-five pounds.
20 to 30	0	0	0	0	0	0	0
30 to 40	3	1	1	0	0	0	0
40 to 50	11	1	3	0	2	0	0
50 to 60	33	2	2	3	0	1	0
60 to 70	35	1	1	3	2	0	1
70 to 80	11	0	1	1	0	0	0
Total	93	5	8	7	4	1	1

Females.

20 to 30	0	0	0	0	0
30 to 40	1	0	0	1	0
40 to 50	18	1	1	2	1
50 to 60	23	1	0	2	1
60 to 70	6	0	0	0	0
70 to 80	4	1	0	0	0
Total	52	3	1	5	2

Periods in Months of Gain in Weight and General Improvement with Amelioration of Symptoms. Of the 145 cases presenting periods of improvement with amelioration of symptoms and gain in weight the improvement occurred in the greatest number of cases for one or two months (that is, in 79 per cent. of all cases) after the beginning of treatment; after this period the number of cases presenting improvement is less and less.

Males.

Years.	Cases without periods of improvement.	One month.	Two months.	Three months.	Four months.	Five months.	Six months.	Seven months.
20 to 30	0	0	0	0	0	0	0	0
30 to 40	3	1	0	2	0	0	0	0
40 to 50	11	3	4	2	1	1	0	0
50 to 60	33	8	13	6	5	1	0	0
60 to 70	35	9	24	2	0	0	1	1
70 to 80	11	5	5	0	1	0	0	0
Total	93	26	44	12	7	2	1	1
Per cent.		17.9	30.3	8.2	4.7	1.4	0.7	0.7

Females.

Years.	Cases with periods of improvement.	One month.	Two months.	Three months.	Four months.	Five months.	Six months.	Seven months.	Eight months.
30 to 40	1	0	1						
40 to 50	18	14	2	0	0	0	0	0	0
50 to 60	23	10	8	2	1	1	0	0	0
60 to 70	6	4	2	0	0	1	0	1	1
70 to 80	4	3	0	0	1	0	0	0	0
Total	52	31	13	2	2	2	0	1	1
Per cent.		2.3	9.5	1.4	1.4	1.4	0	0.7	0.7

Latent Cancer. There were 12 cases (1.2 per cent.) in which the disease was unsuspected or in which the symptoms due to the associated disease were so marked and the gastric symptoms so slight or absent that the disease was unsuspected or only detected shortly before death. The cases in this class are arranged in the following table according to age and sex and according to the suspected disease.

Males.

Years.	No. of cases.	Unsuspected.	Chronic nephritis.	Arterio-sclerosis.	Anemia.	Cardiac disease.	Tuberculosis.
40 to 50	1	0	0	0	0	0	1
50 to 60	2	0	0	0	1	1	0
60 to 70	3	1	1	1	0	0	0
70 to 80	2	0	1	1	0	0	0
Total	8	1	2	2	1	1	1

FEMALES.

Years.	No. of cases.	Chronic nephritis.	Arterio-sclerosis.	Anemia.	Cardiac disease.
40 to 50	1	0	0	0	1
50 to 60	1	1	0	0	0
60 to 70	2	0	1	1	0
70 to 80	0	0	0	0	0
	4	1	1	1	1

DYSPHAGIA. Dysphagia existed in 69 instances, namely, in those cases in which the growth involved the cardiac orifice, that is, in 6.9 per cent. of all cases. Of the 69 cases, 60 per cent. represented males and 40 per cent. females. The following table includes the number of cases presenting this condition among males and females arranged according to age:

Years.	Males.	Per cent.	Females.	Per cent.
20 to 30	0	.0	0	.0
30 to 40	2	2.8	0	.0
40 to 50	4	5.6	6	8.6
50 to 60	17	24.6	10	14.5
60 to 70	11	15.9	7	10.2
70 to 80	18	11.2	4	5.6
Total	42	60.1	27	38.9

LOSS OF WEIGHT. Of the 1000 cases the weight on admission was noted in 839 instances. Of this number 743 (98.5 per cent.) presented a loss of weight of from five to seventy-eight pounds.

PAIN. Of the 1000 cases pain was present in 931 (93.1 per cent.).

Effect of Food on Pain. Of the 931 cases with pain the symptoms appeared immediately after taking of food in 191 cases (20.5 per cent.); several hours after meals in 83 instances (9.9 per cent.), and in 616 instances (66.1 per cent.) it was not influenced by food, while in 41 cases 4.4 per cent. it appeared irregularly, at times bearing some relation to the ingestion of food and at other times not. This condition is to be contrasted with our cases of ulcer in which there were 940 cases with pain; this symptom appeared within the first hour after meals in 223 instances between one and two hours in 188, after two hours in 491, and in 38 it appeared irregularly.

Relation of Pain to Acidity. Of the 733 cases in which the gastric secretion was examined pain appeared in 672 (91.5 per cent.).

	Cases.	Absent.		Moderate.		Moderately severe.		Severe.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Normal acidity	23	2	0.2	1	0.1	8	1.1	12	1.7
Hyperchlorhydria	35	3	0.4	5	0.7	10	1.4	18	2.6
Hypochlorhydria	21	4	0.5	3	0.4	5	0.7	11	1.6
Anacidity	654	52	7.0	112	16.6	136	20.2	351	52.2
	733								

The relation of pain to acidity is presented in the table above, from which it is evident that pain is more pronounced in those instances associated with a low acidity. The reverse is true in cases of ulcer in which pain is most pronounced in those cases associated with high acidity, as is observed in the following table:

	Cases.	Absent.		Moderate.		Moderately severe.		Severe.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Normal acidity	376	2	0.2	92	11.3	123	15.1	159	19.6
Hyperchlorhydria	246	1	0.1	8	9.0	35	4.3	202	24.9
Hypochlorhydria	188	7	0.7	59	7.3	82	10.1	40	5.0
	810								

Location of Pain. In 561 instances of all of the 931 cases affected with pain the pain extended more or less over the whole abdomen; it was limited to the epigastric region in 229 instances; in 68 to the lower abdomen; in 62 to the back, and in 11 to the chest.

Tenderness. Of the 1000 cases, tenderness was present in 893 cases (89.3 per cent.). The tenderness was localized in special areas in 265 cases (26.5 per cent.), and was general over the entire abdomen in 628 (62.8 per cent.). This condition is to be contrasted with that found in ulcer in which of the 1000 cases epigastric tenderness was present in 908 cases (90.8 per cent.). A tender area was noted to the right of the median line in 41 cases (4.1 per cent.); a dorsal, together with an epigastric, tender spot in 523 instances (52.3 per cent.); a dorsal area alone in 25 (2.5 per cent.).

Anorexia. Anorexia was present in 893 of our 1000 cases, or 89.3 per cent. The symptoms varied markedly from a slight loss of appetite to an absolute aversion for food. The 893 cases are divided into 516 males and 377 females. The following table illustrates the degree of anorexia among males and females according to age:

Years.	Males.								Females.							
	Slight.		Moderate.		Intense.		Variable.		Slight.		Moderate.		Intense.		Variable.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
20 to 30	1	0.1	0	0	1	0.1	0	0.0	0	0	0	0	0	0	0	0
30 to 40	4	0.4	6	0.6	7	0.7	2	0.4	2	0.2	5	0.5	3	0.3	2	0.2
40 to 50	36	4.0	25	2.8	31	3.4	4	0.4	41	4.5	20	2.2	59	6.6	13	1.4
50 to 60	51	5.7	89	9.9	76	8.6	18	2.0	31	3.4	51	5.7	44	4.9	7	0.7
60 to 70	21	2.3	56	6.2	45	5.6	12	1.3	11	1.2	16	1.6	34	3.8	5	0.5
70 to 80	9	1.0	4	0.4	16	1.8	2	0.2	6	0.6	8	0.8	17	1.9	2	0.2
Total	122		180		176		38		91		100		157		29	

Effect of Food on Vomiting. Vomiting is a prominent symptom, occurring in 893 (89.3 per cent.). This symptom appeared immediately after the ingestion of food in 182 (20.3 per cent.); several hours after meals in 74 (8.2 per cent.), while in 599 cases (67 per cent.) it was not influenced by food, and in 38 (4.2 per cent.) it appeared irregularly, seeming at times to bear some relation to the ingestion of food and at times not.

Vomiting and Pain. Of the 931 cases with pain vomiting occurred in 862 instances (92.6 per cent.). Of the 931 cases in which pain appeared there were 191 having pain immediately after meals, of which 158 had vomiting. There were 83 with pain several hours after meals, of which 76 had vomiting. There were 616 not influenced by the ingestion of food, of which 593 had vomiting, and in 41 instances the pain appeared irregularly, of which 35 had vomiting.

The following table illustrates this condition:

Time of appearance.	Cases with pain.		Cases with vomiting and pain.		Per cent. of cases of vomiting in comparison with cases with pain.
	No.	Per cent.	No.	Per cent.	
Immediately after meals	191	20.5	158	18.3	82.7
Several hours after meals	83	8.9	76	8.8	91.5
Not influenced by meals	616	66.1	593	68.7	96.2
Appearing irregularly	41	4.4	35	4.0	85.3
Total	931		862		

In the 69 cases of cancer not accompanied by pain, vomiting occurred in 31 cases (45 per cent.). In our cases of ulcer the vomiting was proportionately more frequently observed in those instances in which pain appeared early, as is observed in the following table:

Time of appearance of pain.	Cases with pain.	Cases with vomiting.	Percentage of cases of vomiting in proportion to the cases with pain.
In one hour	223	194	87.0
In one to two hours	188	143	76.6
After two hours or irregularly	529	324	61.2
	940	661	

Relation of Vomiting to Acidity. Of the 733 cases in which the gastric secretion was examined, vomiting appeared in 655 (89.3 per cent.). The relation of vomiting to acidity is illustrated in the accompanying table, from which it is apparent that by far the largest proportion of cases with severe vomiting are associated with anacidity.

	Total cases.	Absent. No.	Absent. Per cent.	Moderate. No.	Moderate. Per cent.	Severe. No.	Severe. Per cent.
Normal acidity	25	1	.01	8	1.2	14	2.1
Hyperchlorhydria	35	4	.05	12	1.8	19	2.5
Hypochlorhydria	21	3	.04	7	1.0	11	1.6
Anacidity	654	70	9.50	191	29.1	393	60.0
	733	78		218		437	

These cases are to be contrasted with the ulcer cases in which vomiting is definitely more prominent in those instances accompanied by high acidity.

Acidity.	Cases.	Moderate vomiting. No.	Moderate vomiting. Per cent.	Severe vomiting. No.	Severe vomiting. Per cent.
Normal acidity	298	125	23.5	171	32.5
Hyperchlorhydria	138	18	3.3	122	22.8
Hypochlorhydria	95	76	14.3	19	3.5

Hematemesis. Gastric hemorrhage occurred in 227 cases (25.4 per cent. of those patients in which vomiting was present, and in 22.7 per cent. of the whole number. The following table presents the cases with gastric hemorrhage arranged according to age and sex:

	Males. No.	Males. Per cent.	Females. No.	Females. Per cent.
30 to 40	2	0.8	1	0.4
40 to 50	41	18.0	14	6.1
50 to 60	94	41.4	18	7.9
60 to 70	49	21.5	3	1.3
70 to 80	3	1.3	2	0.8
Total	189	83.0	38	16.5

The following table presents the proportion of cases according to age, accompanied by a single hemorrhage, and those by multiple hemorrhages; 88.7 per cent. of these cases presented multiple hemorrhages and but 10.8 per cent. single hemorrhages.

Years.	Cases.	Per cent. of cases with hemorrhages.	Proportion of cases with single hemorrhages. No.	Proportion of cases with single hemorrhages. Per cent.	Proportion of cases with multiple hemorrhages. No.	Proportion of cases with multiple hemorrhages. Per cent.
30 to 40	3	1.2	0	0	3	1.3
40 to 50	55	24.1	5	2.0	50	22.0
50 to 60	112	49.3	11	4.8	101	44.4
60 to 70	52	22.8	8	3.4	44	19.3
70 to 80	5	2.1	1	0.4	4	1.7
Total	227	99.5	25	10.8	202	88.7

To be contrasted with these cases are the cases of ulcer in which a much larger proportion of cases were accompanied by single hemorrhages (38.7 per cent.) and but 60 per cent. with multiple hemorrhages. Of the 227 cases with hematemesis the hemorrhages were small in 151 cases, profuse in 62, and variable in 14. The blood was coffee-ground or dark in 202, bright red in 18, and variable in 7.

MELENA. Tar-colored stools or a history of this condition was present in 189 of the 1000 cases, that is, in 18.9 per cent. In the following table is illustrated the number and percentage of these cases at various ages, the largest proportion appearing between the fiftieth and sixtieth years:

Years.	Cases with melena.	Percentage of cases with melena
30 to 40	1	0.1
40 to 50	46	4.6
50 to 60	97	9.7
60 to 70	43	4.3
70 to 80	2	0.2
Total	189	18.9

These cases are to be contrasted with the same condition occurring in ulcer in which tar-colored stools occur much more frequently, that is, in 51.5 per cent., the largest proportion appearing between the tenth and thirtieth years. Noting the proportion of cases with melena in comparison with those with hematemesis it is evident, as is illustrated in the following table, that gastric hemorrhage is much more frequent than melena:

COMPARISON OF CASES WITH HEMATEMESIS AND MELENA AT VARIOUS AGES.

Years.	Gastric hemorrhage. Cases.	Gastric hemorrhage. Per cent.	Melena. Cases.	Melena. Per cent.
30 to 40	3	0.3	1	0.1
40 to 50	55	5.5	46	4.6
50 to 60	115	11.2	97	9.7
60 to 70	52	5.2	43	4.3
70 to 80	5	0.5	2	0.2
Total	227		189	

If these cases be contrasted with those of ulcer it is evident that in ulcer the reverse condition exists, that is, melena is over twice as frequent as gastric hemorrhage.

Occult Blood. The test for occult blood in the stools was rarely omitted. The feces were examined in 642 of the 1000 cases. Of these a positive reaction was obtained in 594 (92.5 per cent.). The examination only included those cases in which visible blood was absent or had not appeared for some time before the test had been made. When once occult blood was observed in these cases it could usually again be found at any time afterward; this is not true of ulcer, for in this latter condition the blood is not always present in the first test, but frequently appears some time during the course of the disease. In the ulcer cases positive tests for occult blood were obtained in 86.6 per cent.

Occult Blood as an Early Sign of Cancer. Of the 642 cases in which tests for occult blood were made in the feces, 216 were early cases. Of these 201 (93 per cent.) presented occult blood, indicating that the presence of occult blood is a very constant as well as early sign of gastric cancer.

Tumors. Of the 1000 cases a mass (tumor) was detected in 719 (71.9 per cent.) some time during the course of the disease. Arranged according to age and sex these cases may be divided as follows:

Years.	Males.		Females.	
	No.	Per cent.	No.	Per cent.
20 to 30	1	0.1	0	0
30 to 40	11	1.1	10	1
40 to 50	98	9.8	103	10.3
50 to 60	175	17.5	133	13.5
60 to 70	108	10.8	47	4.7
70 to 80	20	2.0	13	1.3
Total	413		306	

Of the 719 cases in which a mass could be palpated 217 presented this condition within six months after the first appearance of symptoms, that is, 30.1 per cent., while in 502 it was presented after six months (69.9 per cent.), from which it is evident that the appearance of a palpable tumor is over twice as common after the first six months after the first appearance of symptoms than before this period.

Location of Growth. From a clinical point of view cancer of the stomach may be divided into those located at the cardia, those

at the pylorus, and those involving the stomach generally. Of the 1000 cases the involvement is as follows:

	No.	Per cent.
Pyloric area	589	59.9
Cardiac area	69	6.9
General involvement	306	30.6
Undetermined	36	3.6
Total	1000	

Divided among males and females and according to age the involvement may be tabulated as follows:

	Males.					Females.				
Years.	No.	Pyloric.	Cardia.	General involvement.	Undetermined.	No.	Pyloric.	Cardia.	General involvement.	Undetermined.
20 to 30	0	0	0	1	2	1	0	0	0	1
30 to 40	23	17	2	2	2	14	8	0	6	0
40 to 50	125	75	4	41	5	136	67	6	61	2
50 to 60	249	157	17	87	8	146	80	10	54	2
60 to 70	143	92	11	34	6	75	36	7	28	4
70 to 80	345	33	8	2	2	40	24	4	10	11
Total	588	374	42	147	25	412	215	27	159	11

Secondary Cancer of the Stomach. Of these there were 9 (0.9 per cent.) in our series; 3 were secondary to breast cancer; 2 were secondary to rectal cancer; 4 were secondary to uterine cancer. The remainder, 991 (99.1 per cent.), were primary cancers.

Dilatation of the Stomach. Dilatation of the stomach was present in 467 instances. Arranged according to age and sex this condition is presented in the following table, indicating that the largest percentage of cases occur in males between the fiftieth and seventieth years of life:

	Males.		Females.	
Years.	No.	Per cent.	No.	Per cent.
20 to 30	0	0.0	0	0.0
30 to 40	3	0.6	1	0.2
40 to 50	52	11.1	61	13.0
50 to 60	147	31.2	72	15.4
60 to 70	89	19.0	31	6.6
70 to 80	5	1.4	6	1.1
Total	296	62.9	171	36.3

Peristaltic movements were observed in 411 cases.

Perforation occurred in 23 cases (2.3 per cent.) of our series.

Arranged according to age and sex these cases may be classified as follows:

Years.	Males. No.	Males. Per cent.	Females. No.	Females. Per cent.
30 to 40	1	4.3	0	0
40 to 50	5	21.7	2	8.6
50 to 60	4	17.3	3	13.0
60 to 70	5	21.7	1	4.3
70 to 80	2	8.6	0	0
Total	17	73.6	6	25.9

Fever. Of the total number of cases, 472 in all, in which the symptoms were noted almost during the entire course of the disease, fever occurred in 203 cases (43 per cent.). Of these 73 ran a temperature of between 99° and 100°, 66 between 100° and 101°, and 45 between 101° and 102°.

Temperature.	No. of cases.	Per cent. of cases.
99° to 100°	73	15.4
100° to 101°	66	13.7
101° to 102°	45	9.5
102° to 103°	13	2.7
103° to 104°	6	1.2
With temperature	203	43.0
Without temperature	269	57.0

Of the 203 cases in which fever was present 37 (18.2 per cent.) had fever during the entire course of the disease; 52 (25.6 per cent.) developed fever during the first six months of the disease, while 151 (74.3 per cent.) first developed fever after the sixth month of the disease. Fever is only present therefore in about 18 per cent. of cases during the entire course of the disease; but 25 per cent. of cases develop fever during the first six months of the disease, and 74 per cent. of the cases develop fever after six months, indicating that fever is a late manifestation of the disease.

Ascites and Edema of the Extremities. Ascites or edema appeared in 211 (21.1 per cent.) of our cases. Ascites appeared alone without edema in 44 cases (4.4 per cent.); edema appeared without ascites in 104 cases (10.4 per cent.); edema and ascites appeared together in 63 cases (6.3 per cent.). Of the 211 cases with ascites or edema but 53 (24.6 per cent.) presented these signs before the first six months after the first appearance of symptoms,

while 158 (74.7 per cent.) presented these signs after the first six months, indicating that both ascites and edema are late manifestations in gastric cancer.

Jaundice. Jaundice was presented in 32 of our cases (3.2 per cent.). It was present as a late manifestation of the disease, in every instance appearing only after the symptoms of the disease had been present for over six months.

Metastases. Metastases were noted in 672 (67.2 per cent.) of our cases; of these:

255 (37.9 per cent.) occurred in the glands.
222 (33.0 per cent.) occurred in the liver.
54 (8.0 per cent.) occurred in the peritoneum.
45 (6.6 per cent.) occurred in the pancreas.
41 (6.1 per cent.) occurred in the intestines.
14 (2.0 per cent.) occurred in the lung.
12 (1.7 per cent.) occurred in the spine.
2 (0.3 per cent.) occurred in the skin.
27 (4.0 per cent.) undetermined.

It is evident that over 70 per cent. of the metastases appeared in the glands and in the liver.

Bowel Movements. The bowels moved normally in 67 cases (6.7 per cent.); diarrhea existed in 249 cases (24.9 per cent.); constipation existed in 572 cases (57.2 per cent.). The bowels were variable, that is, constipation alternating with diarrhea in 112 cases (11.2 per cent.).

Mental Condition. Of the 1000 cases depression of more or less severe type was noted in 861 instances (86.1 per cent.). Of this number actual melancholia was observed in 9 instances (0.9 per cent.). The depression is usually noted early in the disease, but becomes more severe as the disease progresses.

Operations. Of the entire number operation was performed in 265 instances (26.6 per cent.). Of this number 138 (51.8 per cent.) were exploratory laparotomies. Gastro-enterostomies were performed in 98 (36.9 per cent.); gastrostomies in 21 (7.8 per cent.), and pylorectomies and gastrectomies in 9 (3.3 per cent.).

Duration of Life Following Exploratory Laparotomy. In the 126 of the 138 cases we were able to follow the cases sufficiently to determine the duration of life following the exploratory incision.

It is evident that death ensues within a year in most instances, and but few cases are observed surviving over a year.

Years.	Males.						Females.					
	For 3 months after operation.	From 3 to 6 months.	From 6 to 12 months.	From 12 to 18 months.	From 18 to 24 months.	From over 2 years.	For 3 months after operation.	From 3 to 6 months.	From 6 to 12 months.	From 12 to 18 months.	From 18 to 24 months.	For over 2 years.
30 to 40	1	1	0	0	0	0	2	0	0	0	0	0
40 to 50	2	2	0	0	2	0	3	6	6	0	1	1
50 to 60	8	14	4	0	2	1	2	9	3	0	1	0
60 to 70	8	7	7	4	1	0	6	0	8	1	0	0
70 to 80	3	2	0	1	0	1	5	0	1	0	0	0
Total	22	26	11	5	5	2	18	15	18	1	2	1

Duration of Life following Gastro-enterostomies. In 7 of the 98 cases the patients could not be followed, and the duration of life of these cases could not be determined. As is evident from the following table the largest proportion of cases die within one year following this operation, though a few survived as much as two years and over:

Years.	Males.						Females.					
	For 3 months after operation.	From 3 to 6 months.	From 6 to 12 months.	From 12 to 18 months.	From 18 to 24 months.	For over 2 years.	For 3 months after operation.	From 3 to 6 months.	From 6 to 12 months.	From 12 to 18 months.	From 18 to 24 months.	For over 2 years.
30 to 40	2	0	0	0	1	0	1	0	0	0	0	0
40 to 50	5	4	5	0	2	1	1	2	2	0	6	3
50 to 60	3	2	6	0	3	3	1	2	2	1	4	0
60 to 70	6	1	7	1	2	1	1	0	1	1	2	0
70 to 80	1	2	0	2	0	0	2	0	1	0	0	0
Total	17	9	18	3	8	5	6	4	6	2	10	3

Duration of Life following Gastrostomy. As is indicated in the following table, most of the cases die within a year after the operation of gastrostomy.

Years.	Males. For 3 months.	From 3 to 6 months.	From 6 to 12 months.	From 12 to 18 months.	From 18 to 24 months.	For over 2 years.	Females. For 3 months.	From 3 to 6 months.	From 6 to 12 months.	From 12 to 18 months.	From 18 to 24 months.	For over 2 years.
30 to 40	0	0	0	0	0	0	1	0	0	0	0	0
40 to 50	0	2	0	0	0	0	1	0	1	0	0	0
50 to 60	3	3	1	0	1	0	0	1	0	1	0	0
60 to 70	1	0	1	1	0	0	1	0	1	0	0	0
70 to 80	0	1	0	0	0	0	0	0	0	0	0	0
Total	4	6	2	1	1	0	3	1	2	1	0	0

Duration of Life following Pylorectomies and Gastrectomies. Of the 9 cases operated on, but one lived for eighteen months after operation.

Years.	Males. For 3 months after operation.	From 3 to 6 months.	From 6 to 12 months.	From 12 to 18 months.	From 18 to 24 months.	For over 2 years.	Females. For 3 months.	From 3 to 6 months.	From 6 to 12 months.	From 12 to 18 months.	From 18 to 24 months.	For over 2 years.
30 to 40	0	0	0	0	0	0	0	0	0	0	0	0
40 to 50	0	1	0	1	0	0	0	1	1	0	0	0
50 to 60	0	1	1	0	0	0	0	2	0	0	0	0
60 to 70	0	0	0	0	0	0	1	0	0	0	0	0
70 to 80	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	2	1	1	0	0	1	3	1	0	0	0

Position of Growth as Determined at Operation or Autopsy. The number of cases observed were 284. Of these the location of the growth is as follows.

	No.	Per cent.
In the pyloric area	166	58.4
In the cardiac area	19	6.6
In the lesser curvature	23	8.1
In the greater curvature	12	4.2
In the fundus	8	2.8
General involvement	56	19.7

Conclusions. From a careful study of the 1000 cases of cancer of the stomach the following conclusions may be drawn:

1. Of patients suffering with various gastric disturbances, 9.6 per cent. are affected with cancer while but 7.8 have ulcers.

2. The largest proportion of cancers occur between the fortieth and sixtieth years of age, while the largest proportion of ulcers occur between the twentieth and fiftieth years.

3. The greatest number of cases occur in males (588 males and 412 females).

4. Of patients affected with gastric cancer there is an hereditary history of cancer in 9.4 per cent.

5. A definite history of trauma occurs in 1.9 per cent. of cases.

6. Anemia is present in 82 per cent.; chronic endocarditis in 11 per cent.; arteriosclerosis in 69 per cent.

7. Seven per cent. give a direct history of former ulcer, and only in 23 per cent. could the cancer have formed from ulcer.

8. A history of overindulgence in food or drink can be obtained in about half the number of cases of cancer.

9. The greatest proportion of cases of cancer present an anacidity, that is, 89 per cent.; 3 per cent. show a normal acidity; 4 per cent. an hyperacidity, and 3 per cent. a subacidity. Lactic acid is present in 81 per cent.; the Oppler-Boas bacilli in 79 per cent.; sarcinæ in 32 per cent.; coffee-ground contents in 61 per cent.

10. The average duration of life is less than one year in 66 per cent. of all cases, between one and two years in 22 per cent., and over two years in 11 per cent.

11. Periods of improvement, including gain in weight, are not uncommonly observed for a short time in cancer of the stomach.

12. Latent cancer occurs in 1 per cent. of the cases.

13. Dysphagia is present in 7 per cent. of the cases and pain the most frequent of all symptoms in 93 per cent. Tender abdominal areas are present in 69 per cent.

14. Anorexia and vomiting are most prominent symptoms, being present in 89 per cent. of cases.

15. Hematemesis is present in 25 per cent. of all cases and melena in 19 per cent. Occult blood appears in the stools in 92.5 per cent.

16. The tumor was sufficiently advanced to be palpable in 72 per cent. of cases, but only in 30 per cent. of these cases within a half year of the first appearance of symptoms, while in 60 per cent. of cases this symptom was manifested after the first six months.

17. Clinically in 60 per cent. of cases the cancer is located at the pyloric area, in 7 per cent. at the cardiac area, and in 30 per cent. there is a general involvement.

18. Ninety-nine per cent. of the gastric cancers are primary and but 1 per cent. represent secondary growths.

19. Dilatation of the stomach occurs in 47 per cent. of cases.

20. Perforation occurs in 2 per cent., and fever in 43 per cent.; ascites and edema in 21 per cent.; jaundice in 3 per cent., and metastases are present in 67 per cent.

21. Operation was performed in 28 per cent. of cases; in 52 per cent. of these there were exploratory laparotomies; in 37 per cent. gastro-enterostomies; in 8 per cent. gastrostomies, and in 3 per cent. pylorectomies and gastrectomies. In but a small proportion of cases did the patients survive over a year after operation.

22. As determined by operation or autopsy the location of the growth was as follows: in 59 per cent. there was pyloric involvement; in 8 per cent. cardiac involvement; in 8 per cent. involvement of the lesser curvature; in 4 per cent. of the greater curvature; in 2 per cent. of the fundus, and in 19 per cent. there was a general involvement.

The early diagnosis of cancer of the stomach is usually quite difficult, for the most important symptoms may be absent even though the growth may have already assumed considerable proportions.

The most important sign of this disease, the presence of a palpable tumor, is observed in 72 per cent. of cases, and yet in 60 per cent. of cases it makes its appearance six months after the first appearance of symptoms, and it cannot therefore be relied upon as an early sign of the disease.

The absence of free hydrochloric acid is a frequent sign, as it is present in 89 per cent. of cases, and yet the condition is so frequent in other conditions that it loses much of its value.

Signs of pyloric obstruction with consequent dilatation are noted at times, and when present early are of the greatest diagnostic importance. According to my experience one of the most constant signs as an early manifestation of the disease is the presence of occult blood in the stools. It was present in 92.5 per cent. of our

cases. The continued occurrence of this sign whenever there is a suspicion of cancer points rather certainly to the presence of this disease.

A history of some previous digestive trouble was observed in 232 cases (23 per cent.). Of these 109 had slight attacks of indigestion for a period of five years or more preceding the present gastric disease, while 25 had slight attacks during the last five years preceding the present disease. Of the remaining 123 cases, 23 had chronic indigestion more or less all of their lives, of which 29 had chronic indigestion mainly during the last years preceding the present illness.

Seventy-three cases gave a definite history of former gastric ulcer. It is therefore evident that in the 1000 cases but 23 per cent. presented a history of any previous digestive disturbance whatever even in the slightest degree, and that but 7.3 per cent. gave a direct history of ulcer. If therefore all of the former digestive disturbances be considered as due to ulcer the formation of gastric cancer from ulcer could not have taken place in more than 23 per cent.; if all of the cases with slight digestive disturbances be disregarded in our series this percentage is reduced even to 12.3 per cent. I therefore believe that from a study of my own cases from a clinical point of view, as well as from the pathological studies of Aschoff, that the figures of Wilson and MacCarty (71 per cent.), so often referred to, are far too high, and that while I am convinced that gastric ulcers are at times transformed into malignant growths, I do not believe that this change takes place in more than 23 per cent. of cases, and possibly is not even so large a proportion.

Of the entire number of my cases, operations were performed in 266 instances (26.6 per cent.). Of these 138 (51.8 per cent.) were exploratory operations. Gastro-enterostomies were performed in 98 (36.9 per cent.); gastrostomies in 25 (7.8 per cent.), and pylorectomies and gastrectomies in 9 (3.3 per cent.). Of these there is not one patient living. It is therefore evident that the early diagnosis of cancer of the stomach is still fraught with difficulty, and that until more certain methods are available exploratory incisions should be urged upon all persons over forty years of age having

gastric symptoms, which are not relieved after a few weeks' treatment, especially is this the case if there be some loss of flesh, an absence of free hydrochloric acid in the gastric contents, and occult blood in the stools. Even under these conditions many cases will be operated on too late, for there can be no question but that gastric cancer may be present for some time and may assume considerable proportions even before marked symptoms of indigestion are manifested. Inasmuch as in a certain proportion of cases gastric ulcers become cancerous, it is well in all operations for gastric ulcers to consider the advisability of performing excision or partial gastrectomy to prevent any possibility of the transition of ulcer into cancer.

SOME RELATIONS OF THE BRAIN AND OF THE OLFACTORY APPARATUS TO THE PROCESSES OF IMMUNITY

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The body is provided with three obvious lines of defense against infection, namely, its peripheral epithelium, its blood and lymph, and its tissue cells. The activity of modern investigators has been engrossed almost wholly with the study of the last two; the first has received very little attention. Yet it is indisputable that the epithelial covering of the body must have intrinsic resources of protection against adverse influences which are in such habitual action that its relations should be considered truly physiological rather than pathological as would be the response to adventitious agencies. In short, a study of the pathologic physiology of the peripheral epithelium must conceive it primarily as a mechanism for the *prevention* of disease rather than, as in the case of the body fluids and tissues, an establishment for producing the means of *cure*. While the protoplasm of the surface cells must be endowed with a degree of autonomy involving capacity for independent response to irritation, possibly including the production of specific antibodies, its striking peculiarity is its abundant supply of sensory nerves, largely endowed with "specific energy," through which every external stimulus is made to provoke an immediate and universal internal response.

The incitement to the following investigation was a desire to develop some immunological relations between the peripheral and the central mechanisms. If *a priori* conceptions are given undue prominence at the outset, a measure of defense may be found in the

wise dictum of Richet[1], that in biologic research the guiding thread must always start from the teleologic point of view.

Modern therapeutics offers abundant illustrations of the beneficent influence of physical agencies acting externally. The criterion for the usefulness of cold water in the treatment of typhoid fever is the "physiological response" which its application may provoke. As Chantemesse points out, the hydriatric stimulus probably does not excite the formation of specific antibodies against the invading noxa, but indirectly through reflex excitement of the various motor and metabolic mechanisms, it seems probable that the *capacity* for the formation of antibodies is enhanced. Similarly, the benefits of the open-air treatment in tuberculosis are in some way due to physiological response to external agents, which in another place I have attempted to show largely exert their influence through the temperature nerves of the skin. In other words, there is good reason to believe that at least the vital capacity for the formation of antibodies is largely under the control of external stimuli which make up the environment of what is known as the "hygienic life." The fact that tuberculosis finds least resistance to its development in the tissues of those who, like the American Indians, from an habitual open-air life are suddenly forced to conform to the restraints of civilization, argues that hygienic living produces no specific antibodies against this disease.

But there is abundant clinical evidence that a great variety of antigens can produce specific anaphylactic systemic response when applied to the peripheral epithelium. The assumption that such antigens must be absorbed into the circulation before becoming effective, while probably generally correct, is unwarranted without direct evidence.

The urticarias and other anaphylactic phenomena following the ingestion of certain articles of food by some people, and especially the asthmatic paroxysms induced by the inhalation of certain odors, belong to one of the most interesting divisions of clinical pathology. Indeed, it was an incident related to me by V. C. Vaughan, Jr., of Detroit, which gave the final impulse to the present investigation.

[1] Ann. de l'Inst. Pasteur, 1907, xxi, 497.

Vaughan's account is as follows: The patient was a man, aged thirty-six years, who was suffering from moderately advanced tuberculous disease of the lungs complicated by recurrent hemoptyses. From March 11 to 13, inclusive, the patient received three injections of fresh, normal rabbit serum of $\frac{1}{10}$ c.c., 9 c.c., and 10 c.c. On April 7, twenty-seven days after the first injection, a rabbit was brought into the patient's room, was handled by him, and allowed to run about the bed. Between three and five hours after this event the patient suffered an asthma-like attack—the first which he had ever experienced. As indicated at the outset, the drift of my conception has been that what are essentially anaphylactic phenomena form a conspicuous feature of normal sensory activity. The mysterious ability of the hound to follow a definite trail unconfused by a multitude of other footsteps is cleared up at once if we assume that the dog's olfactory apparatus is sensitized to the odor which he follows. One is tempted to suggest that even the phenomena of complementary color sensation as manifested in the "after-images" are but the psychic signs of specific antibodies formed in the retina.

The experiments to be described were performed upon guinea-pigs. Sensitization was achieved by subcutaneous injection of normal horse serum obtained from a commercial firm. The sensitizing dose usually varied from $\frac{1}{4}$ to $\frac{1}{2}$ c.c. in quantity. The toxic injection was invariably given through the jugular vein. Many intracranial operations were performed, including cutting of the olfactory nerves or ablation of the olfactory lobes with or without a certain bulk of the anterior cerebrum. The guinea-pig is anatomically excellently adapted for such work. As is well known, the anatomical relations of the sense organ for smell are almost unique.[1] The olfactory sense organ is constructed peripherally of nerve cells inclosed within the olfactory mucous membrane. Processes directed distally from the nerve cells project freely like bristles from the free surface of the membrane, while from the opposite poles "teledendrons" find their way into the cranial cavity to embrace nerve cells of the olfactory lobes.

This research would have been quite impossible but for the devoted

[1] Cf. Troland, Amer. Jour. Physiol., 1913, xxxii, 19.

aid given by my colleague, Dr. Cuthbert Powell, who has freely lent his surgical skill to the performance of the many scores of surgical operations involved in the investigation.

Guinea-pigs sensitized to horse serum may be desensitized by sojourn in a horse stable. The first effort made was to elicit some sign of anaphylaxis in the peripheral epithelium of a serum-sensitized animal. A guinea-pig which had received a subcutaneous injection of horse serum thirty-eight days before was held gently upon its back and horse serum in small droplets was allowed to fall into either nostril. I expected to witness some sign of specific irritation. The result, however, was wholly negative. The animal received a few hours later an intravenous injection of $\frac{1}{2}$ c.c. of horse serum and died in about three minutes with characteristic symptoms.

Another sensitized pig was made to inhale finely vaporized serum, in the manner to be described later, but, as in the first case, the results were negative. These observations were repeated on numerous occasions with different animals and the results all pointed to the conclusion that *guinea-pigs sensitized by subcutaneous injections of horse serum manifest no particular irritation when the same serum is instilled for the first time into the nose or given by inhalation.*

It then occurred to me that possibly the aroma of the animal producing the sensitizing antigen might develop some characteristic reaction. Accordingly, four guinea-pigs were placed in a box covered with wire netting. Two of the animals were normal and two had received each $\frac{1}{2}$ to $\frac{3}{4}$ of 1 c.c. of serum subcutaneously forty days previously. The box was carried to a livery stable containing a score or more of horses on July 7. The air of the stable at this time was powerfully impregnated with a characteristic odor and there was a particularly pungent quality to the smell. Later in the season, as cooler weather advanced, the intensity of the odor diminished and its pungent quality disappeared. There was, as will be seen directly, a coincident change in the biological reactions. To resume, the box had been in the stable possibly five minutes when marked nervous disturbances were manifested by the two sensitized animals. One of them, a female weighing 480 gms. showed marked excitement, dashing about the box and biting at her companion, and then scratched the nose vigorously.

These symptoms subsided in about half an hour. The other sensitized pig, weight 195 gms., lay prone or squatted upon the floor of the box and emitted plaintive sounds. The animals were kept in the stable overnight and appeared wholly normal when removed next morning. The control animals showed no particular disturbance.

Some drops of serum were instilled into the nostrils of the smaller sensitized pig and provoked within a few moments somewhat the same reactions as the animal had manifested in the stable. This experiment was, under these conditions, unfortunately not repeated. More than twenty-four hours after its introduction into the stable and about eight hours after its removal therefrom, the larger sensitized pig was given by the vein nearly 1 c.c. of horse serum. *There was no marked reaction;* soon after its release from the holder the animal fed as usual. Twenty-five days later this pig received another intravenous injection of serum and died within four minutes. The smaller of the two sensitized pigs received its toxic dose some twenty-eight hours after removal from the stable. Owing to difficulties in manipulation a great excess of serum was injected into the vein, probably more than 1 c.c. The animal did not suffer the usual shock, but died from respiratory failure in about half an hour; its lungs were nearly completely collapsed when the chest was opened.

In the light of later observations I am inclined to think that this animal's death was a sign of the passing of the phase of anti-anaphylaxis induced by inhalation of stable air combined with the excessive magnitude of the toxic injection. No effort was spared, of course, in seeking a solution of the results obtained in these preliminary experiments. Of fundamental importance appeared to be the question whether the desensitizing agent in the air of the stable affected the body indirectly through action on the olfactory mucous membrane or was absorbed directly through the respiratory tract. To resolve this question groups of pigs, sensitized or normal, were operated for section of the olfactory nerves. Under ether, a small hole was trephined just posterior to the cribriform plate, the nerves were cut with a fine bistoury, and their stumps wiped out with a small pledget of cotton held in forceps. The animal manifests little or no disturbance after such an operation. In other animals not

only the olfactory nerves were removed but the olfactory lobes as well. But, for reasons that will be detailed later, this more extensive operation was necessarily performed only on normal, non-sensitized animals.

The experimental data are condensed in the following tables:

EXPERIMENT. Four sensitized guinea-pigs, two with intact olfactories, exposed to stable August 18.

1. Male, 480 gms.; olfactory nerves excised July 12, sensitized with serum July 16. No reaction in stable.

2. Male, 645 gms.; sensitized July 16. Olfactory nerves excised August 15; restless after twenty minutes in stable.

3. Male, 675 gms.; unoperated, sensitized July 16. Much erotic excitement after fifteen minutes in stable.

4. Male, 750 gms.; unoperated, sensitized July 16. No reaction except slight uneasiness after forty minutes in the stable.

After remaining all night in the stable each animal received on August 19 an intravenous injection of upward of $\frac{1}{2}$ c.c. of fresh serum. Every pig died in characteristic shock except number 3, which responded to the injection with violent struggles, some respiratory rales, deepened respiration and rubbing of the nose when released. After this moderate shock the pig completely recovered.

One cannot fail to connect the excitement of this pig when exposed to the stable, attempting to copulate with his male companions, etc., with the desensitization certified by the development of anti-anaphylaxis. This animal was reëxposed in the stable thirty-three days later when he showed but slight excitement and the following day he succumbed to an intravenous injection.

EXPERIMENT. Two pigs received subcutaneous serum July 16. Exposed in stable August 20.

1. Male, 525 gms. Olfactories intact. Within five minutes after entering stable is erotic and continues restless, scratches nose, etc., for an hour.

2. Male, 540 gms. Olfactory nerves had been cut July 12, and a serum inhalation given August 16. In the stable is restless, slightly dyspneic, and scratches chin during an hour.

August 21 intravenous injection of serum, more than $\frac{1}{2}$ c.c., was given to each. Pig 1 had two slight spasms, sneezed twice, and then recovered. Pig 2 showed very little reaction. Result, anti-

anaphylaxis in both animals. The recovery of the second animal would appear to show that the olfactory apparatus was not concerned in the desensitization, but on August 22 its brain was exposed for the purpose of excising the olfactory lobes; it was then found that the olfactory nerves appeared to have regenerated in the interval of thirty-nine days elapsing between the nerve section and the stable exposure.

EXPERIMENT. Two pigs sensitized July 16. Both had been in the same box with those of a former experiment. They were placed again in the stable for forty minutes on August 22. Twenty hours later they received the toxic injection.

1. Male, 660 gms. Somewhat erotic and restless in stable.
2. Male, 360 gms. Olfactory nerves cut July 12. Restless and rubs nose in stable.

Both died from the toxic injection which, it will be noted, was given twenty hours after leaving the stable, whereas the usual interval was two or three hours. Autopsy on the second pig indicated partial regeneration of the olfactory nerves.

EXPERIMENT. Two pigs sensitized July 16. Placed in stable for five hours August 25.

1. 425 gms. A comparatively feeble animal, is restless, rubs nose, and scratches in the stable.
2. 790 gms. Olfactory nerves were cut on August 24. Less excitement shown in the stable than in the case of pig 1.

Intravenous injections of more than $\frac{1}{2}$ c.c. of serum were given within an hour of removal from the stable. Pig 2 died promptly from shock. Pig 1 showed no reaction except for temporary muscular weakness becoming apparent in an hour. This animal was undoubtedly anti-anaphylactic, but was found dying the next moring after exposure to the cold of the previous night. It was frequently noted that guinea-pigs recovering from the strain of anaphylactic shock are exceedingly non-resistent to external cold. Their temperature regulation is apparently profoundly disturbed.[1]

It is unnecessary to go further into detail along this line of evi-

[1] Cf. Doerr, in Kolle u. Wassermann's Hdb. d. pathogen. Mikroörg, 2 Aufl. Bd. ii, Th. 2, 1070.

dence. Suffice it to say that a large proportion of guinea-pigs sensitized subcutaneously to horse serum were desensitized by exposure to the air of the horse stable. There was a very obvious relation between the pungency of the stable odor and the latent period of anaphylactic disturbance. When the smell was most intense the nervous symptoms of anaphylaxis came on almost immediately. In Denver the nights become strikingly cool in August so that the more intense stable odor only endured for two or three weeks in July and the time required to sensitize guinea-pigs did not allow of prolonged investigation under conditions most favorable to olfactory stimulation.

As the mean temperature of the air fell and the stable odor became less intense the latent period of anaphylactic disturbance increased from a very few minutes to a quarter of an hour, then to longer periods and finally the onset of disturbance could not be distinguished. Nevertheless sensitized pigs kept in the stable for a day or more sometimes proved to be anti-anaphylactic to intravenous injection even when they had manifested no striking symptoms marking desensitization.

All the earlier observations pointed to the conclusion that only pigs possessing intact olfactory mechanism were subject to desensitization through the stable air. Obviously a single positive result demonstrating anti-anaphylaxis in the case of a smell-free guinea-pig would show that the noxa producing desensitization could affect the body through channels other than the olfactory. Such a demonstration was afforded by observations on four animals kept in the stable for three days during the first week in October. Each had suffered either recent section of its olfactory nerves or loss of both olfactory nerves and lobes many weeks previously. Submitted to the test of intravenous inoculation, one of the pigs whose olfactory lobes had been excised thirty-nine days before and which had been sensitized by subcutaneous serum thirty-six days before, recovered from the toxic injection after slight symptoms of shock.

This section of my work may be briefly summarized by stating that fourteen sensitized guinea-pigs with intact olfactory sense were exposed to the stable. Of these, five became completely anti-anaphylactic to the intravenous toxic injection and two succumbed

only after evidence of great resistance to the toxic dose. The fourteen pigs include two that had been previously made anti-anaphylactic as witnessed by recovery from an intravenous injection; both died from the second intravenous dose. The fourteen pigs also include two in which the olfactory nerves had been cut long before but which seemed to have regenerated.

Ten sensitized pigs were exposed in the stable after recent section of their olfactory nerves or long-standing ablation of the olfactory lobes. None of these had manifested any marked symptoms of anaphylactic disturbance in the stable. Only one of this group survived the toxic intravenous injection.

Daily communion with such phenomena as have been described is bound to give rise to certain more or less defensible impressions which have not been submitted to definite proof. Of this nature are the notions that the desensitizing agent in the stable air operates on the body in two ways: (1), acutely, as an odor irritating the olfactory nerves with the production of anaphylactic symptoms and (2), more slowly, by absorption through the respiratory tract, without the production of striking anaphylactic symptoms. The important question as to whether anti-anaphylaxis can be produced by the mere local odorous stimulation of the olfactory epithelium has not been settled, although the facts seem to point in that direction. The phase of anti-anaphylaxis in these experiments, as found in other fields, comes on very soon after exposure to the exciting cause. Also, several experiments pointed to the conclusion that the anti-anaphylactic period is very short—that it is rapidly vanishing within twenty-four hours after removal from the desensitizing environment.

It having been proved that fully developed sensitization could be temporarily undone by exposure of animals to stable air, the conclusion seemed obvious that sensitization should be altogether prevented in pigs kept in the stable during the latent period of sensitization. The result of an appropriate experiment proved, however, directly the contrary, as follows:

Experiment. Five guinea-pigs, weighing about 350 gms. each, were placed in the stable October 24, about twenty hours after receiving sub-

cutaneous injections of serum, with the exception of one animal, which had received an injection ten days before. This last pig was taken from the stable October 29, that is, fifteen days after its sensitizing injection, and at the end of five days' residence in the stable. An intravenous injection given at this time was fatal within four minutes. The remaining four pigs were taken from the stable November 7, after exposure of fourteen days, and each succumbed to an intravenous injection within about three minutes. Autopsy was performed on these, as in all other fatal cases, and the lungs were found in characteristic anaphylactic distention.

Guinea-pigs of this group manifested a somewhat striking difference in behavior from all other animals exposed in the stable. They never recovered from the timidity associated with the change of environment nor did they acquire a normal appetite for food.

The results of the experiment indicate that, at least in cool weather, the processes leading to sensitization go on in the environment which may effect desensitization of a fully sensitized animal.

Sensitization to horse serum is not caused by exposure to stable air. As to the nature of the agent producing the desensitizing effects, I have no definite evidence. When the box containing the guinea-pigs was held directly under the nose of a horse, or when the manure impregnated straw of the stable was placed within it no particular reaction was observed. An effort was made, of course, to sensitize the guinea-pigs to horse serum by the same influence which caused their desensitization.

The two normal pigs which had been used as controls and exposed to stable air on July 7 received each an intravenous injection of $\frac{1}{2}$ c.c. of horse serum sixty-three days later. There was nothing like shock to be discerned, though one of the animals rubbed its nose vigorously ten minutes after its release, the other seemed sleepy and both preened the body as if stimulated by itching.

Four normal pigs, all males and weighing about 390 gms. each, were placed in the stable September 9. One of them was removed after twenty-four hours and within an hour thereafter received an intravenous injection. There was no reaction except that the animal remained rather unusually quiet. For fourteen days the remaining pigs were kept in the stable, two of them being taken out for some hours each day. One of these and the third pig—which had been continuously in the stable, were given intravenous injections within

about an hour after removal with completely negative results. The evidence shows that while the possibility of minor degrees of sensitization to toxic injections of serum cannot be denied, nothing like the sensibility leading to fatal shock is induced.[1] The slighter degrees of anaphylactic reaction are somewhat uncertain in significance since the normal pig is prone to manifest the same actions, such as nose-rubbing and preening the body.

Anaphylactic shock and desensitization caused by operations upon the brain of the sensitized guinea-pig. According to the well known views of Besredka,[2] sensitization in the guinea-pig is primarily or wholly a property of the brain.

This author holds the view that during the process of sensitization the body tissues form a substance "une sensibilisine" (known elsewhere as "allergin"), which fixes itself to the brain cells.

Intracerebral injections of a large dose of serum ($\frac{1}{4}$ c.c.) produces rapid desensitization with great shock or death. With small intracerebral injections ($\frac{1}{4\,0\,0}$ c.c. to $\frac{1}{4\,0}$ c.c.) desensitization of the cerebrum comes gradually and the animal becomes anti-anaphylactic. The animal is resensitized by a new injection made within the period. He holds that the condition of anti-anaphylaxis is a return to the normal state. Guinea-pigs may be desensitized by intracerebral injections but cannot be sensitized thereby, that is, the brain cells cannot prepare the sensitizing substance. In an animal thoroughly narcotized by ether the intracerebral injection of serum produces no shock but still induces anti-anaphylaxis.

That brain sensitization cannot altogether account for the phenomena of anaphylactic shock was sufficiently demonstrated by Auer and Lewis[3] who found that sensitized guinea-pigs were killed by intravenous injection and showed characteristic distention of the lungs after section of the vagi nerves and destruction of the base of the brain, medulla, and spinal cord.

That the irritability of the brain is profoundly modified by the

[1] Not until this work had been long completed did I learn that Rosenau, in an announcement I have not been able to trace, describes successful efforts to sensitize guinea-pigs in a horse stable.

[2] Ann. de l'Inst. Pasteur, 1907, xxi, 117; ibid., 777, 950; ibid., 1910 xxiv, 273, 879; etc.

[3] Jour. Exp. Med., 1910, xii, 151.

state of sensitization was early made clear in our experiments. In attempting to remove the olfactory sense from sensitized pigs in preparation for the stable experiments, it was found that while intracranial section of the olfactory nerves produced no particular reaction, ablation of the olfactory lobes caused profound disturbance, as illustrated in the following experiment:

EXPERIMENT. Four guinea-pigs, weighing about 730 gms. each, were given subcutaneous injections of $\frac{1}{3}$ c.c. serum July 16. On August 15, under light ether anesthesia, the olfactory nerves were cut and wiped out in three; there was no special reaction. In the fourth pig, which received least ether of all, both olfactory lobes and nerves were removed. After its release the animal continued to lie on its side and in about fifteen minutes severe clonic convulsion of the limbs appeared, lasting half an hour or more. The animal gradually recovered but still, more than two hours after the operation, the pig manifested rhythmic "bucking" movements of the body without the feet leaving the floor. This animal was well next day and was given $\frac{3}{4}$ c.c. serum intravenously; there was no reaction except for slight torpor. One of the first three pigs was given a like injection immediately afterward and died within three minutes.

It should be said that removal of the olfactory lobes in a normal guinea-pig produces no definite response. The shock and subsequent anti-anaphylaxis described are no special effect of removal of the olfactory lobes, but follow mutilations of the cerebrum, thus:

EXPERIMENT. A vigorous male pig, weight 700 gms., sensitized July 16. On August 23, under ether, an amount of cerebral tissue was removed from the parietal regions equalling in bulk about one and a half times that of the olfactory lobes. The animal when released continued to lie on its side for ten minutes, with clonic twitching of the hind legs continued for some time. The next day this pig received an intravenous injection of $\frac{3}{4}$ c.c. of serum and, with the exception of slight asthmatic wheezing, showed no special reaction.

EXPERIMENT. Male pig, 780 gms., sensitized July 14. On August 21 a bulk of cerebrum equalling five or six times that of the olfactory lobes was removed. For nearly an hour the pig lay on its side with clonic twitchings, increasing to convulsions, of the legs. It springs and bucks after sitting up and then for many hours carries on continuous, coördinated forced movements, seeking always to escape restraint and wander forward. The next morning the animal was found dead. The fatal result was probably brought about partly by failure to react to the lowered temperature of the night air.

Numerous experiments of like character have definitely proved that anaphylactic shock is caused by mutilation of the brain in the sensitized guinea-pig. The degree of shock seems rather strictly related to the amount of cerebral tissue removed, but varies much in different animals. The intensity of shock suffered after a definite nerve injury seemed to diminish as the weather became cooler. If this impression is confirmed it may be elucidated by the facts portrayed in the following section of this paper. In the accounts[1] of anaphylactic shock and the resulting phase of anti-anaphylaxis usually given, the phenomena have been induced by reinjection of the antigen causing sensitization, but here are examples of profound somatic changes being induced by mere ablation of brain tissue in amounts whose loss would cause no particular disturbance in a normal animal. In seeking an explanation it seemed probable that the effective stimulus consisted in the mechanical agitation of the brain. To test this view an electric vibrator, designed for therapeutic massage, was used, its flat, ebonite disk, rapidly oscillating, being firmly applied for three minutes to the skulls of a series of sensitized guinea-pigs which were slightly etherized. The results showed a curious discrepancy.

EXPERIMENT. A guinea-pig already described, which had received a subcutaneous injection of serum July 16, had lost part of its cerebrum on August 23, and had recovered from an intravenous injection August 24, was submitted to skull vibrations on September 22. The only reaction to the vibration was rubbing of the nose and a slight "steppage" movement. On September 23 more than $\frac{1}{2}$ c.c. of serum was given intravenously, resulting in dyspnea, peristalsis, and cough, but recovery within an hour. (This animal received another vibration November 9, followed by intravenous injection November 11, from which it recovered. Another intravenous injection was given fourteen days later, with likewise recovery, and a fifth intravenous injection was made December 9, without producing symptoms. This is a case of either prolonged anti-anaphylaxis or permanent immunity.)

EXPERIMENT. Guinea-pig, male, weight 820 gms. Sensitized July 16. From August 16 to August 31 received five inhalations of vapor of horse serum without effect. On September 2 the electric vibrator was applied to the skull for some five minutes. There was no reaction except "steppage"

[1] Cf. Doerr, op. cit., 1085.

movements, nose rubbing, and slight incoördination. The next day the animal received intravenously $\frac{3}{4}$ c.c. of serum and fully recovered, with slight symptoms. Twenty days later the olfactory lobes were removed. The shock was intense. The animal never fully recovered, though it would eat greedily; it died four days after the operation.

The results of subsequent experiments indicate that desensitization caused in the foregoing animals by vibration of the skull was dependent in some way on the treatment they had previously received auxiliary to the primary sensitization. Five other guinea-pigs, two of which had been sensitized intravenously, were submitted to vibration and all died in shock when injected the following day by the vein. Two of the animals received before the toxic injections no less than six vibration-treatments at intervals of two days. The application of the vibrator to the skull is exceedingly drastic treatment and frequently resulted in complete inhibition of the respiration and great slowing and enfeeblement of the heart beat. The phase of anti-anaphylaxis produced by the shock of brain operations is very short. It passes off in less than forty-eight hours, as was evidenced by three special experiments which it is not necessary to detail.

That no shock is occasioned by moderate ablation of nervous tissue in the normal pig is shown by the following:

Experiment. Normal male, 360 gms. November 3, removed olfactory lobes and a portion of the anterior cerebrum slightly greater in bulk. There was no reaction whatever. (In two days this pig sickened, probably from infection, and died in a week. Other normal pigs suffered loss of much greater quantity of brain without permanent disturbance.)

In a widely quoted paper Schürer and Strasmann[1] describe experiments in which they attempt to controvert Besredka's idea that the sole seat of the anaphylactic reaction is in the brain. They excised the whole brain, including the basal ganglia, in sensitized guinea-pigs and then gave them serum by intravenous injection. The animals died within a few minutes to several hours, and the results were supposed to controvert the notion that the brain is involved in ana-

[1] Zeitsch. f. Immunitätsf., 1912, xii, 143.

phylactic phenomena. In the light of the observations described above it is plain that such methods are necessarily incompetent to clear up the subject.

Desensitization of the brain through section of the olfactory nerves. On one occasion, the olfactory lobes were removed from a fully sensitized guinea-pig, but the animal manifested no sign of shock whatever. In seeking the cause for this departure from the rule that had seemed established it was found that this pig had, eight days before, been subjected to section of its olfactory nerves. It at once became necessary to follow out the suggestion aroused by this development.

Experiment. Six young pigs, weighing about 270 gms. each, were sensitized by subcutaneous injection August 29. From four of these, 1, 2, 3, 4, the olfactory nerves were cut and wiped out on September 16 under very slight etherization. There was no reaction except to a very slight degree in one (pig number 2) in which bleeding occurred through the nose due to injury to the cribriform plate. On September 24, twenty-six days after subcutaneous injection, the olfactory lobes were removed from pigs 1, 2, and 5 (the latter having intact olfactory nerves). Pigs number 1 and 2 showed not the slightest shock; pig number 5 lay on its side for nearly ten minutes, with somewhat convulsive clonic trembling of the legs. This shock did not produce anti-anaphylaxis, for the animal succumbed to intravenous injection the next day. On September 25 the olfactory lobes were excised from pig 3. There was no shock whatever, the animal sitting up at once when released, though it rubbed its nose and preened the body. On the same date there was taken from pig 4 (olfactory nerves destroyed September 16) both the olfactory lobes and a portion of the anterior cerebrum about equal in bulk to the combined olfactory lobes. The animal lay quietly on its side for two minutes after release from the holder, breathing hard, but without convulsive movements, and then sat up with normal appearance except for slight, temporary spasmodic nodding of the head. No anti-anaphylaxis was produced, for the animal succumbed to an intravenous injection next day. September 25, pig number 6, sensitized but with intact olfactory nerves, was made to lose its olfactory lobes, and a portion of the anterior cerebrum equal to a single olfactory lobe. When released this animal lay on its side for five minutes with clonic convulsions. It then sat up and appeared normal for awhile, but soon became restless and the subject of forced movements which continued until the animal died in convulsions, attended with enormous erections of the penis, after six hours. At autopsy the lungs were found collapsed, containing a few hemorrhagic areas but no consolidation.

The experiments show very definitely that in sensitized guinea-pigs the nervous shock following mutilation of the brain is greatly reduced eight or ten days after section of the olfactory nerves. It was sought to determine how soon such desensitization of the brain followed upon nerve section, and how long it continued.

Experiment 1. Male pig, 440 gms. Sensitized August 29. Olfactory nerves destroyed September 24. Next day the olfactory lobes were removed. The animal manifested moderate but decided reaction, such as relatively slow recovery from the operation, followed by nose rubbing and clonic tremblings and humpings of the body. The shock was not sufficient to produce anti-anaphylaxis, for the pig succumbed in three minutes next day to toxic injection.

2. Female pig, far advanced in pregnancy, 910 gms. Sensitized August 29. Olfactory nerves cut November 5. On November 6 the olfactory lobes and a similar bulk of cerebrum were removed. There was scarcely any shock following the operation, the only sign of anaphylaxis being a slight inspiratory humping of the body setting in ten minutes after release.

These results indicate that while the desensitizing effect upon the brain of olfactory nerve section may develop within a day the full influence of the deprivation of olfactory stimuli is not established with certainty till later.

Experiment. Male pig, 500 gms. Sensitized August 29; olfactory nerves cut November 5. On November 18 excised olfactory lobes and a similar bulk of cerebrum. The animal lies quiet for nearly ten minutes after release, and then sits up with no evidence of reaction except for slight rhythmic lifting of the legs. Next day the pig succumbed in three minutes to the toxic injection.

It is clear from these experiments that the diminished sensibility of the brain following section of the olfactory nerves in sensitized guinea-pigs may be well marked within twenty-four hours and remains in full force for at least thirteen days. After longer periods there may always be suspicion of regeneration of the olfactory nerves. In the following experiments part of the cerebrum was removed long after ablation of the olfactory lobes:

Experiment. Female pig, 690 gms. Olfactory lobes removed August 27, and the space left filled with melted paraffin (in none of several cases in which this was done could the paraffin be detected with certainty after

several weeks). Serum was injected subcutaneously August 29. On November 3, sixty-eight days after removal of the lobes, under slight ether anesthesia, there was scooped from the anterior cerebrum an amount of tissue estimated to equal about twice the bulk of the normal olfactory lobes. There resulted moderate but distinct shock, with some forced movements passing off after about thirty minutes. Two days later the animal withstood an intravenous injection of nearly $\frac{1}{2}$ c.c. of serum, with scarcely any reaction.

This experiment indicates that after removal of the olfactory lobes (of course including the attached nerves) the sensitiveness of the brain to laceration has been more or less completely restored in about two months. Similar conclusions were derived from other experiments, the conditions of which were more complicated, which it is unnecessary to describe.

It might be claimed that the influence upon the irritability of the brain apparently exerted by the olfactory sense is not a specific property of this sense but is wielded by any strong sensory impulse or is also a part of the function of other special senses. I did not fully grasp, until too late to sensitize new animals, the importance of testing the relation of the visual sense to cerebral irritability. However, a single experiment went to show that the removal of one eye does not desensitize the brain as after section of the olfactory nerves.

Experiment. Male, weight 615 gms. Sensitized by intravenous injection of $\frac{1}{2}$ c.c. of serum on September 6. Under ether anesthesia the left eye-ball was removed November 6. On November 10, under ether, the olfactory lobes and an equal bulk of cerebrum were removed. There was moderate but pronounced shock lasting for more than half an hour. The shock was not sufficient to protect the pig with anti-anaphylaxis when an intravenous injection was given next day.

From the results that have been described in the last two sections of this work it seems impossible to avoid the conclusion that sensitization of the brain and sensitization of the body represent different biologic conditions. The former is a labile, the latter a stabile state. The threshold of irritability of the sensitized brain is plainly levelled in response to olfactory sensory stimuli. The brain may be completely desensitized without affecting in the least the response of the body to the second toxic dose of the antigen. An attempt

to elucidate the teleological significance of these coördinations will be made in the discussion at the end of this paper.

As is well known, Besredka claims that the intracerebral injection of $\frac{1}{4}$ c.c. of serum will, in an unanesthetized, sensitized guinea-pig, cause speedy anaphylatic death. If the conclusions drawn above as to desensitization of the brain following section of the olfactory nerves be correct it should be possible for an animal so treated to resist Besredka's fatal injection. That this is true is proved by the following:

Experiment 1. Female pig, 360 gms. Sensitized August 29. Olfactory nerves were cut and wiped out September 16. On September 26, under light ether anesthesia, a trephine hole was made over the cerebrum and there was injected through a hypodermic needle into both hemispheres a total of $\frac{1}{4}$ c.c. of horse serum. The animal was practically out from under the influence of ether during the injection. There was but very slight reaction marked by restlessness and some jerking of the head. This animal weighed 450 gms. November 5, when it received an intravenous injection and died in four minutes.

2. Female pig, 840 gms. Sensitized August 29. Olfactory nerves cut November 5. On November 8 the skull was trephined over the posterior cerebrum and the animal was released until entirely recovered from ether; then, as before, $\frac{1}{4}$ c.c. of serum was injected into the brain. There was rather severe shock, marked by clonic twitchings of legs, rapid breathing, circular movements, weakness of hind legs; gradual recovery after an hour or two. This shock was not sufficient to produce anti-anaphylaxis, for the animal succumbed next day in the usual way to intravenous injection.

Besredka found that intracerebral injections made with very small amounts of serum, or made under deep ether anesthesia are not lethal and the following day the animal is found to be anti-anaphylactic. Rosenau and Anderson[1] repeated these experiments on etherized guinea-pigs and found that seven out of eight animals died from the second injection given next day. These discrepancies may be accounted for by supposing that the duration of the anti-anaphylactic state may be less as well as greater than twenty-four hours.

According to the foregoing argument, it should be suspected that ether narcosis affects only the susceptibility of the brain to shock,

[1] Jour. Med. Res., 1908, xx, 37.

leaving that of the body unaffected. It was found, in fact, that a sensitized guinea-pig etherized to relaxation died as quickly from intravenous injection of serum as one treated without an anesthetic. In the earlier experiments of this work the intravenous injections were all given without an anesthetic for fear of the masking of anaphylactic symptoms; but in all the confirmatory tests the animals were subjected to a slight etherization, with little or no distortion of reactive symptoms. Reference was made to an impression which developed as a result of prolonged experimentation that the anaphylactic shock caused by the ablation of a definite mass of brain tissue became less intense as the weather turned cooler. Such a result might be expected if the olfactory sense, whose excitation probably varies with the external temperature, be indeed, a physiological regulator of brain irritability. Doerr[1] summarizes his discussion on the site of anaphylaxis thus: "Das die wesentlichen Angriffstellen der anaphylaktischer Noxa in der Peripherie liegen, ist heute wohl über allen Zweifeln sichergestellt."

The relation of the olfactory nerves to shock in the normal brain. The marked dependence of anaphylactic disturbance following operations on the brain of serum-sensitized guinea-pigs upon integrity of the olfactory nerves raises the question whether in the normal animal there is not a specific physiological relation between the olfactory sense and irritability of the brain. The literature of cerebral physiology makes it obvious that so profound a problem can only be solved by a great number of guarded observations. Nevertheless, a few experiments were ventured in this field and the results were sufficiently positive to deserve record.

Five guinea-pigs were taken which were in very fair condition, although they had been inoculated with what was evidently an attenuated strain of tubercle bacilli nearly three months before. In three of the animals the olfactory nerves were cut and two or three days later the olfactory lobes were excised together with a quantity of cerebral tissue estimated at three times the bulk of the lobes. In making this estimate the olfactory lobes were placed upon a sheet of paper and three heaps of equal size, scooped from the

[1] Hdb. d. path. Mikroörg, Bd. ii, H. 2, 1078.

anterior cerebrum were laid nearby. The operations were performed, as usual, under very light anesthesia. As will be seen, the symptoms of shock were much more pronounced in the two animals whose olfactory nerves remained intact up to the time of the operation.

EXPERIMENT. 1. Weight 600 gms. Excised olfactory nerves November 13. On November 15 excised olfactory lobes and about three times their bulk of cerebrum. Pig when released lay for ten minutes apparently conscious, but with clonic tremblings of the legs and slight dyspnea. Recovers quickly; result, very slight reaction.

2. Weight, 485 gms. November 13 olfactory nerves cut. On November 16 the olfactory lobes and part of the cerebrum removed as before. The animal lay quietly for six minutes and then sat up without reaction, except for some dyspnea, nose-rubbing, and rhythmic nodding of the head. Result, very slight reaction.

3. Weight, 510 gms. Olfactory nerves cut November 16. On November 18 olfactory lobes and three times their bulk of cerebrum removed. Animal tries to sit up in six minutes after release. There are no convulsive movements but the animal runs about the room and seeks to hide in a dark corner. Normal but dull within an hour. Result, slight reaction as shown by apparently forced movements.

4. Weight, 510 gms. Olfactory nerves remain intact until time of the main operation, November 15, when the olfactory lobes (with nerves) and three times their bulk of cerebral tissue were removed. Pig lay for more than ten minutes after release, with clonic tremblings. It then turns on back with convulsive doubling of the body. Still unable to sit up in twenty minutes, after which there is a convulsive twisting of the body, with legs kicking. Recovers soon after. Result, marked but moderate reaction.

5. Weight about 580 gms. Olfactory nerves intact until main operation, November 16, when the olfactory lobes and cerebral tissue were excised as before. Pig lay for ten minutes after release, with clonic tremblings of the legs; then there was a tetanoid twisting of the body. Sits up in twenty minutes and manifests apparently forced twisting movements. Within forty minutes the only disturbance is shown by rhythmic lifting of the body. Result, marked but moderate reaction.

In answer to the objection against the use of ether in these experiments it may be said that narcotization was of such light degree that animals in which the olfactory nerves alone were cut would sit up at once without reaction on release from the holder. When nerve-cell tissue was excised the animal lay on the side, with or

without convulsive twitchings, for a period apparently proportional to the amount of substance removed; that is, the symptoms were a result of the operation, not of the anesthesia.

Influence of Cocainization of the Nose on the Shock from Intracranial Operations. The suggestive surgical conceptions of Crile[1] are recalled by these results and an effort was made to modify the shock of brain operations through an attempt to cocainize the olfactory mucous membrane. It is well known that a solution of cocaine sprayed into the nose may completely abolish temporarily the sense of smell. Only a few, unconvincing experiments were tried in this direction. A 2 per cent. solution of cocaine was dropped into the nostrils of two sensitized guinea-pigs four times in the course of fifteen hours. Then under light ether anesthesia the olfactory lobes and a somewhat greater amount of cerebral tissue were removed from each. There resulted moderate, but distinct reaction in each. The shock was much less and cleared up sooner than was found to be the case in most sensitized pigs subjected to the same operation without cocaine. Each of these animals succumbed next day to intravenous injection. Of four young pigs weighing about 240 gms. each, from a sensitized mother, two were treated with several nasal instillations of cocaine. One of these pigs quickly died with symptoms to be detailed later. The other three were subjected to the loss of the olfactory lobes and about three times their bulk of cerebral tissue. There was decidedly less prolonged convulsive reaction in the cocainized pig than in the untreated pigs, though the former showed a high degree of nervous excitement. From the results of observations already detailed it is obvious that cocaine anesthesia should be prolonged for a day or two in order to obtain its desensitizing action, if any, on the brain.

Certain Analogies between the Effects of Cocaine Poisoning and Anaphylactic Shock. Guinea-pigs were killed by nasal instillation of cocaine and by subcutaneous and intravenous injection. Five unsensitized pigs were given cocaine in about 4 per cent. solution in the vein. Whether the poison was injected slowly or rapidly the result was the same, a speedy diminution in the amplitude of

[1] Boston Med. and Surg. Jour., 1910, clxiii, 893.

respiratory movement and death without convulsion. The heart continued beating for many minutes after respiratory arrest just as it does in anaphylactic death. The lungs were found collapsed at autopsy.

Three young pigs, offspring of sensitized mothers, weighing 180 to 240 gms. each, were killed by the repeated instillations of a 2 to 4 per cent. solution of cocaine in the nose. The symptoms of poisoning came on very suddenly. The animal would fall on its side; the head was tonically retracted, frequently there was well-marked opisthotonus, and there were clonic convulsions of legs and body. The same series of events transpired when subcutaneous injections of cocaine were given. This was done in the case of seven animals, four of which were serum sensitized, but the element of respiratory disturbance was more marked than when the poison was given by the nostrils. The retraction of the head was a characteristic symptom, the chest would be distended and the respiratory movements very rapid and so shallow as to be hardly visible. An animal might recover after remaining more than half an hour apparently *in extremis*. The convulsive phenomena witnessed in these animals were exceedingly suggestive of those seen in severe anaphylactic shock. But the particular object of these experiments was to follow out an observation that had been made on the pig, from a sensitized mother, which had first succumbed to cocaine by the nose. The lungs of this animal were found, postmortem, to be markedly distended, almost as much so as after anaphylactic shock. In two other cases this extraordinary postmortem distention of the lungs was found, although usually the lungs were well retracted from the heart on the ventral side but maintaining apparently a condition of semi-expansion dorsally. In two normal pigs killed by cocaine subcutaneously the postmortem lung distention was less striking than in the sensitized offspring of sensitized pigs. That the postmortem distention of the lungs did not depend upon the terminal convulsions seemed evidenced by the state of two sensitized pigs which were injected with strychnin; in these the lungs were found completely collapsed at autopsy. The expanded lung after death from cocaine offers marked differences from the expanded lung after anaphylactic death. The former is pale, the latter congested.

Both remain distended when excised, but the former scarcely crepitates and scarcely collapses when squeezed in the fingers, the latter does both. In that minority of cases in which the lung remains distended after death by cocaine, its behavior suggest a rubber-like structure.

The phenomena described in this section recall the similar, though still more striking, effects described by Dale and Laidlaw[1] as following the injection into guinea-pigs of *β-iminazolylethylamin.* They call attention to the anaphylactic-like changes produced by this substance.

Reactions of Guinea-pigs to Horse Serum Administered through the Nose and by Inhalation in Sprays. Local and General Anaphylaxis. Comparatively few investigations seem to have been made with a view to determining the effect of the application of antigens to the unaltered peripheral epithelium. The reaction of the tuberculin test of v. Pirquet involves wounding of the outer skin. Administration of antigens by feeding, especially by means of the stomach-tube, greatly complicates the experimental conditions. In an important paper Dserzgowsky[2] describes experiments in which the toxin of diphtheria was applied to the mucous membrane of the nose in plugs of cottonwool moistened with it, and to the general respiratory tract through the inhalation of sprays. Experiments were performed on horses and on the author himself. It was claimed that in these ways active immunity, both local and general, could be harmlessly induced.

Blumenau,[3] following this suggestion, inserted tampons moistened with diphtheria toxin, diluted to one-third strength, into the nostrils of children for thirty minutes. After twenty such treatments diphtheria antitoxin was found in the blood. Practically the same result was obtained by Scheweleff[4] in experiments on dogs. A. C. Klebs,[5] in his history of smallpox inoculation, mentions an ancient custom among the Chinese of protecting against smallpox by putting its virus into the nose.

[1] Jour. of Physiology, 1911, xliii, 182.
[2] Zeitsch. f. Immunitätsf. (abst.), 1910, iii, Th. 2, S. 602.
[3] Ibid., 1910, iv, 353.
[4] Ibid., 1910, x, 1085 (Ref. Bd.
[5] Bull. Johns Hopkins Hosp., 1913, xxiv, 69.

Busson[1] describes experiments in which guinea-pigs sensitized to horse serum were inclosed in a tight box and made to inhale a finely divided spray of horse serum, diluted ten times, for a period of two hours or more. As far as the description can be understood there were very slight but positive signs of anaphylactic reaction. The rise of temperature within the box and the deterioration of the quality of the air must have introduced important complications into the experiment. My results confirm, in general, those of this author. Schlecht[2] records a series of researches showing that injection of a foreign serum into the body causes a great, temporary, increase in eosinophiles of the blood, in guinea-pigs of the mast cells as well, due to increased activity of the bone marrow. The administration of spray-inhalations of horse serum to guinea-pigs, either sensitized or normal, was followed by a high grade of eosinophilia localized in the lungs.

In the discussion on the last paper, Schittenhelm said that he has not been able to repeat the results of Friedberger who had produced aseptic pneumonia by inhalations of serum in sensitized guinea-pigs.

Ishioka[3] made injections of serum through a fine cannula directly into the trachea of sensitized guinea-pigs. Out of forty animals two died at once in anaphylactic shock, the others showed symptoms, but recovered. In a few cases there was produced interstitial pneumonia with much emphysema. In most cases there resulted true lobar pneumonia indicated by patches of infiltration which could even involve a whole lobe.

My method of bringing the serum in contact with the respiratory epithelium differed radically from that described elsewhere. Some two dozen guinea-pigs were treated in two groups; to one fresh horse serum was instilled into the nose by dropping from a hypodermic needle; to the other it was caused to be breathed as a fine spray. In the first case the animal was gently held by the hand upon its back; from an all-glass hypodermic syringe with easily moving

[1] Wiener klin. Woch., 1911, Nr. 43, S. 1492.

[2] Kong. f. innere Med., 1912, xxix, 416; also, Deutsch. Arch. f. klin. Med., 1910, xc, 308; ibid, 1912, cviii, 405; Archiv. f. Exp. Path. u. Pharmakol, 1912, lxvii, 137.

[3] Deutsch. Arch. f. klin. Med., 1912, cvii, 500.

piston and a coarse, blunted needle, small droplets of serum to the amount of $\frac{1}{4}$ to $\frac{1}{3}$ c.c. were allowed to fall upon one or the other of the nostrils. As a rule, only one side of the nose was utilized at each sitting. Various animals were treated daily or at intervals of one, two, or three days.

The serum spray was produced in a commercial "vaporizer" actuated from a compressed air-tank. The spray thus formed was exceedingly fine and resembled the vapor from a gently boiling tea kettle. A funnel made of stiff paper was applied over the nose and mouth of the guinea-pig as it sat upon a table. The nozzle of the spray apparatus was closely applied within the smaller but open end of the funnel. The spray was applied at intervals similar to those of the instillations, and the sittings lasted, as a rule, about three minutes. The serum was often used in full strength; in dilutions of one-half or one-quarter strength the results appeared the same. Theoretical objections against this method of procedure seem invalid in the light of the reactions obtained.

Each group of guinea-pigs was subdivided into four. The members of one subdivision were normal animals; those of another had been sensitized by the subcutaneous injection of serum; those of another were unsensitized but had weeks before been relieved of their olfactory lobes; and finally there were those which had been subcutaneously sensitized after removal of the olfactory lobes.

Special Reactions to the Nasal Instillation of Serum. When horse serum is slowly dropped as described into a nostril of a guinea-pig for the first time there is usually no disturbance whatever; the fluid is quickly sucked into the nose, and not until a considerable quantity has been introduced is there any expulsion, which is evidently mechanical in character. Late in the sitting, taste and probably swallowing motions are manifested. The nasal canal in a medium-sized guinea-pig has a length of nearly 5 cm. and therefore it is not likely that the first droplets reach the pharynx. Even with the second treatment, after two days, signs of active resistance to the instillation of serum may appear; active sniffing movements, except that they are expiratory, more or less resist the entrance of serum or expel it from the nostril.

These minor phenomena are physiologically significant but are

difficult to interpret because they may occur with the instillation of normal saline or solutions of cocaine at the very first administration. It was noted, however, that active resistance to the instillation of serum appeared uniformly earlier in animals with intact olfactories than in those deprived of their olfactory lobes. In animals treated every alternate day my notes record signs of great nasal irritation in normal pigs at the second instillation, while in specimens without olfactory lobes it was not until the fourth treatment, after six days, that active reactions were produced.

Previous subcutaneous sensitization had no perceptible influence in accelerating the reactions. One definite response to the instillation, undoubtedly reflex in character, was regularly obtained from certain animals. This was an excess of salivary secretion. While the mouths of practically all pigs showing signs of irritation against the serum became unusually moist, in a certain number saliva would well up between and drool from the lips. This reaction held constant in the same pigs through a prolonged series of observations. The reaction was usually positive in normal pigs. It was, however, obvious that saliva accumulating in the mouth was frequently removed by swallowing and thus failed to be noted. The reaction can hardly be regarded as other than a sign of specific sensitization. It occurred both in animals previously subcutaneously sensitized and normal, whether with or without olfactory lobes.

It did not occur through the instillation of salt solution when constantly produced by serum. A single nasal instillation with serum evidently induces sensitization. Thus, on October 11, two normal guinea-pigs received $\frac{1}{4}$ c.c. of serum each in both nostrils. The only effect witnessed was the excitement of taste movements. Sixteen days later, October 27, the treatment was repeated. There was now considerable nasal irritation as shown by sniffing and active expulsion of serum from the nose, rubbing of the nose with the paws, and in each case saliva welled from the mouth. Two days later, October 29, one of these animals received an intravenous injection of serum; there was *no reaction*. Five other nasal instillations were given to each pig from November 12 to November 20. The resulting symptoms were the same as those elicited on October 27, except that now the animal which had not received the

intravenous injection ceased to respond to the instillation by the secretion of saliva. Finally, on November 23, both animals received intravenous injections and both died in typical shock. This account anticipates my discussion, but clearly indicates that *local sensitization of the nasal mucous membrane may occur independently of and precede general sensitization.*

The symptoms thus far described as resulting from the nasal instillation of serum are minor reactions which it is possible to confuse with those following non-specific stimuli. But there were extraordinary results obtained in the case of a single animal which though obviously somewhat dependent on idiosyncrasy, are detailed because they differ only quantitatively from reactions characteristic of this group of experiments. A guinea-pig weighing 435 gms. was treated by the nostrils every second day. During the tenth treatment, eighteen days after the first, the animal suddenly choked, loud rattling rales with occasional cough accompanied the deep and labored respiration. The phenomena strongly suggested those of the severest form of bronchial asthma in man. It was several hours before the pig recovered sufficiently to eat. It had been noticed that spasmodic, partial closure of the nostril had resisted the intake of serum. Subsequent administrations of serum each second day provoked similar, though milder symptoms, an excessive salivary secretion becoming a relatively more prominent reaction. The symptoms could not have been due to the flow of serum directly into the trachea, they appeared while still too small a quantity of serum had been applied. Later results with other animals leave no doubt as to the anaphylactic character of the disturbance.

The Effect of the Inhalation of Serum Sprays. The statement was made at the outset that the initial exhibition of vaporized serum, according to the method described, provoked no symptoms whatever. Guinea-pigs previously sensitized by subcutaneous injection reacted apparently as negatively as did normal animals to the inhalation. A remarkable difference, however, presented itself in the behavior of those guinea-pigs which received the serum inhalation after a course of serum instillations by the nostrils. In these cases there was an immediate response to the first inhalation in the way

of a violent dyspnea and with occasional cough, asthmatic in its urgency, but characterized by rapid respiratory movement. The attack would develop suddenly within almost a minute of beginning inhalation and would not subside for from thirty minutes to several hours. Unfortunately no attempt was made to determine whether a phase of anti-anaphylaxis succeeded recovery from the attack of dyspnea. Repetitions of inhalation at intervals of two days or more invariably provoked the same response.

Experiment. Two young pigs were treated every third and every fourth day by instillation of serum in the nose from May 28 to July 12. In the one case on July 17 and in the other on August 7 serum inhalations were given. Both animals exhibited the reaction described, namely, violent, rapid dyspnea, interrupted with occasional deep breaths and cough.

These, together with subsequent observations make it clear that local sensitization of the nasal mucous membrane to horse serum may be induced without the excitement of any very marked reaction. An animal thus peripherally sensitized responds immediately to serum inhalation with characteristic dyspnea, while one sensitized subcutaneously does not. My friend Dr. Hillkowitz kindly tested the blood, drawn from the heart, of one of the animals described for precipitins to horse serum. The dilutions used were 1 to 1000 and 1 to 10,000. The results were negative, as might have been expected from the similar observations of Rosenau and Anderson.[1] An excellent opportunity seemed presented in these animals to determine whether the olfactory mechanism played any role in the serum reactions.

Experiment. One of the pigs, female, weight 645 gms., which had regularly responded to the inhalation, had its olfactory nerves divided August 25. Four days later, and during subsequent exposures, the serum inhalations produced identical symptoms as when the olfactory nerves were intact, though possibly the latent period of reaction was longer. On September 2, the olfactory lobes were excised in this pig without special reaction (because of previous section of the nerves). Two days later a serum inhalation provoked the characteristic dyspnea setting in after the vaporization of thirty or forty drops of serum. On September 10 this animal succumbed in less than five minutes to the intravenous injection of 0.5 c.c. of serum.

[1] Hygienic Laboratory Bull., No. 29, 1906.

It was clear in this case, and abundantly confirmed later, that the peripheral application of serum not only sensitized in a peculiar way the peripheral respiratory epithelium, but produces general sensitization as well. These results were to have been anticipated from the findings of other observers using different methods.

General body sensitization develops gradually during a course of local treatment with serum and apparently is preceded by the acquisition of local anaphylaxis. An effort was made to trace the development of the reactions of local and general anaphylaxis.

Experiment. Two normal male pigs, weighing 360 gms. each, on October 11, were made to inhale with intermissions, for about ten minutes, the vapor of a 50 per cent. dilution of serum. There was slight temporary dyspnea, undoubtedly mechanical in origin, and due to the long exposure to the vapor (the usual treatment occupied three minutes or less and the specific reaction commonly occurred within a minute or two). On October 26, fifteen days later, the pigs having increased in their weight, a similar less prolonged treatment was given. There was no specific reaction, although pig 1 breathed hard for awhile ten minutes later. By October 29, three days after the second, and eighteen after the first inhalation, pig 2 received without ether, $\frac{1}{2}$ c.c. of serum intravenously. There was no reaction whatever. On November 12 both pigs were again sprayed with serum, 50 per cent. dilution. Almost at once pig 1, which had not received the intravenous injection, was seized with violent, rapid panting. This passed off in about fifteen minutes. Three days later this pig was found dead in the morning. I cannot account for the fatality except as a result of the treatment combined possibly with low resistance to the cool air of the night. Autopsy showed the olfactory lobes apparently much softened. The lungs were collapsed and congested but without hemorrhagic areas. Pig number 2, which had received intravenous injection October 29, received four serum inhalations from November 15 to November 20. No dyspnea was caused by either treatment. This animal was given injection of serum by the vein on November 23, and died with violent convulsive and bucking seizures.

These observations show that a single inhalation of serum by a normal guinea-pig provokes, when repeated fifteen days later, hardly perceptible anaphylactic response. A third spraying, performed seventeen days after the last, produces a well marked reaction. Intravenous injection of serum during these observations may have prevented, it certainly did not exaggerate the reactions. It was

found, as might have been expected, that guinea-pigs treated in precisely the same manner showed more or less individual differences in behavior. In contrast to the results of the last series of experiments, the following observations shows that possibly response to the local application of the antigen may be intensified by previous general sensitization.

EXPERIMENT. Male, weight 570 gms. Olfactory lobes removed August 26 and the space left filled with melted paraffin. Sensitized subcutaneously with $\frac{1}{3}$ c.c. serum August 29. Received a prolonged inhalation of serum spray September 25, followed by no specific reaction. Inhalation was given again on October 10, fifteen days later. There immediately resulted a violent rapid dyspnea which had not disappeared after an hour. The treatment was repeated three times on alternate days, with identical response, except that the latent period of reaction increased to a minute or two.

This experiment demonstrates again that response to the inhalation does not demand an intact olfactory apparatus.

I will now review rapidly the history of eighteen guinea-pigs including individuals which were subcutaneously sensitized or normal and with olfactory lobes intact or removed. Half were treated primarily with instillations of serum into the nose and half with serum inhalations. Each group was subdivided into two, in one serum was dropped into the nose for four times on alternate days and in the other for four times every fourth day. The result was more or less active reaction with minor symptoms such as have already been described. After a resting interval of twelve days since the last treatment of the first group and of six days since the last treatment of the second group, all of the nine "instillation" pigs were again given serum by the nose. There was now added in the case of certain animals, to the local symptoms of local irritation and salivary secretion a more general reaction marked by more or less obvious dyspnea together with rattling, apparently bronchial, rales. Of two pigs in which the latter symptoms appeared, both had been subcutaneously sensitized and one had lost its olfactory lobes. Both rales and dyspnea were manifested only by animals which had received serum by the nose every fourth day. It is worth noting that when the group of animals treated in four sittings

by dropping serum into the nose were again given a like treatment eighteen days after the first dosage the anaphylactic shock was much more marked in animals which had received the preliminary instillations every fourth day. In a parallel series of observations carried out with spray-inhalations, the reverse was the case; the strongest reactions occurred in animals receiving the four initial inhalations on alternate days. Five of the "instillation pigs" were given inhalations of serum on the day following the treatment which had produced so marked a reaction. The result was the production of a marked specific dyspnea in two of these animals. It is worth noting that of two pigs which had received no serum subcutaneously and from which the olfactory lobes had been removed, one responded to the spray with dyspnea and one did not. Of the two unoperated pigs, likewise without subcutaneous serum, neither responded. This experiment shows again that local sensitization of one part of the respiratory tract involves sensitization of the rest, though, as will be pointed out presently, there are marked local signs distinguishing the dyspnea produced by inhalation of serum in spray from that caused by its instillation in the nose.

Rapid dyspnea was the one sign of anaphylaxis observed in the inhalation experiments. It could be produced in nearly all animals but some individuals responded much more readily than others. An animal made dyspneic by the inhalation failed to react when sprayed daily until the eighth day when it responded again. In general, the daily administration of inhalations produced no response, though one pig which had received its first inhalation about two weeks before responded each time to inhalation given every forty-eight hours. Of four animals which had received four sprayings on alternate days October, 10 to 16, only one had shown marked reaction. They received another inhalation October 26, and each responded strongly—in fact the dyspnea in two cases was of desperate urgency. Of these animals only two had been sensitized with serum subcutaneoulsy. One of them had been deprived of olfactory lobes; the same operation had been suffered by one of the remaining pair.

Five pigs which had received four inhalations from October 10 to 22, were likewise treated with the spray on October 26, but all

responded very feebly. These animals were again given inhalations on November 2, and the dyspneic response was decidedly more vigorous, though still much less marked than in the group treated after a longer passive interval. These results suggest, of course, the similar findings when anaphylaxis is studied through subcutaneous injections given at close intervals.

In a previous experiment it was shown that guinea-pigs sensitized by dropping serum into the nose could be made dyspneic at once by subjecting them to a spray of serum. The converse of this experiment was now performed. Four pigs that had reaction with dyspnea to the spray were given serum by the nose. In one there was only reaction with minor symptoms, but in the other three there developed after long latent periods, five to ten minutes, rattling rales, which seemed to emanate both from the bronchi and the nose; there was also more or less cough.

As already mentioned, there is a marked difference in the quality of the anaphylactic response to the serum spray and serum instillation. In animals subjected to the former there are no rales, however violent the dyspnea. In animals responding strongly to the latter, rales, which may be very loud and lasting, may occur with a variable element of dyspnea. The difference depends, probably, on the volume of secretion excited. In other words, when a pig sensitized by instillation responds to the spray it is with a dry dyspnea; when a pig sensitized by the spray responds to instillation of serum droplets it is with a moist dyspnea. In later observations it was found in the shock resulting from the toxic intravenous injection, that the influence of the "local sign" of the site of sensitization still held good. A pig which had been sensitized by the spray, in its anaphylactic throes breathed very fast but developed no rales. Others which had been sensitized by instillation developed rales with, usually, less rapid breathing under the same conditions.

All the animals employed in these experiments were finally submitted to the supreme test of intravenous injection of serum. By this means it was sought to determine if or to what degree sensitization of the body could be developed by the peripheral application of serum and also whether such application could essentially modify sensitization already induced by serum injected under the skin.

The intravenous injections were given twenty-nine to thirty days after beginning of the local treatment and after general sensitization had certainly been secured. Of the twenty and more animals available, four survived the first intravenous injection of serum.

Of eleven pigs treated by nasal instillation of serum three survived the first "toxic" injection. One of these belonged to a group of three from which the olfactory nerves and lobes had been removed but which had received no serum subcutaneously. This animal had been given serum by the nose four times at intervals of four days. October 9 to 21, and again on October 27. The creature had manifested plain signs of sensitization. Treated with serum spray October 28 it became violently dyspneic. It was given $\frac{1}{4}$ c.c. of serum intravenously on November 10. The animal was badly shocked in a manner peculiarly different from the ordinary anaphylactic seizures. That is there were no clonic convulsions but the respiration was exceedingly rapid and made audible by rales. After about an hour, when the animal had apparently recovered, it suddenly suffered a fleeting twisting convulsion of the body. Thirteen days later, November 23, this animal received a second intravenous injection of more than $\frac{1}{2}$ c.c. of serum. There was great shock with no sign of convulsion except for clonic twistings at the onset. The respiration was very rapid and bronchial and nasal rales were loud. Finally, after sixteen days, December 9, a third intravenous injection of about $\frac{3}{4}$ c.c. of serum was given. There was no anaphylactic reaction but great muscular weakness. Slight clonic twitchings set in after several hours, the weakness increased, and the animal died in about twenty hours.

Animals of this class differed from those in ordinary anaphylactic shock, also, in that they appeared to be conscious even while lying on the side in deepest shock.

Of the other two "instillation pigs" that survived intravenous injection, both belonged to a group of three normal animals which had neither been operated on or received serum subcutaneously. Their local treatment was similar to that of the last animal described except that neither was sprayed. Both of these animals, especially the second, had manifested slight but apparently unmistakable anaphylactic reaction to serum dropped into the nose. The first

of the two was given $\frac{1}{3}$ c.c. serum intravenously November 8. The creature remained phenomenally quiet throughout the injection. There was no reaction whatever. The injection was repeated with $\frac{1}{2}$ c.c. of serum November 24; result, violent convulsions and typical death. I am inclined to interpret this case as further evidence that local sensitization may be achieved without producing any demonstrable general sensitization. The second surviving pig of this lot had especially reacted to instillation of serum by abundant secretions of saliva, an apparent sign of sensitization. Given an intravenous injection of $\frac{1}{2}$ c.c. of serum on November 23, there was no reaction whatever (the animal was a female far advanced in pregnancy). Sixteen days later, the animal having borne a litter of young a week previously, a second intravenous injection nearly $\frac{1}{2}$ c.c. of serum was given. There was no reaction except for rapid, jerky breathing and a few rales. Special stress deserves to be laid on the fact that this animal had achieved its wonderful power of self protection by a course of treatment which had provoked exceedingly slight signs of anaphylaxis.

The single "inhalation pig" that survived an intravenous injection of serum belonged likewise to a group of three which had neither been subcutaneously sensitized nor operated on. This animal did not react to repeated inhalation treatments until several had been given, then the response was slight but positive as to anaphylaxis. $\frac{1}{2}$ c.c. of serum was given intravenously November 8. The reaction was moderate but distinct. At the outset respiration was deepened and there were slight convulsive movements. Then the breathing became very rapid, interrupted by occasional very deep breaths, and so continued for half an hour. There were no rales as in the instillation pigs. November 24, sixteen days later, the treatment was repeated. Deep rapid respiration with strangling cough came on at once. The animal died in five minutes *without having exhibited respiratory rales or any convulsions.*

It will be noted that none of the animals which had been previously sensitized by the subcutaneous administration of serum survived the toxic injection. The conclusion is that general sensitization so produced is not essentially modified by the efficient antigen applied to the peripheral epithelium, although general sensitization is undoubtedly achieved in this way.

That this non-interference of the serum peripherally applied with the previous general sensitization is not dependent on the time intervals of its application seems shown by the fact that six "instillation" and four "spray" pigs received a course of seven daily treatments extending to within three days of the toxic injection, only one survived it. In other cases the interval between the last local treatment and the toxic injection extended to more than twelve days. It is clear also, that the olfactory apparatus, as far as represented by the olfactory lobes and intracranial nerves is not essential to the systemic effects of serum locally applied. In fact, the normal animals apparently resisted general sensitization in an active way except as to the secretion of saliva. Of a group of animals reacting in about the same way to local treatment, one might survive and the others succumb to the toxic injection. There was nothing in the results obtained by me to suggest any change in the respiratory epithelium resembling the "phenomenon of Arthus" (increasingly morbid local changes following repeated subcutaneous injections), and which has been carefully investigated by Nicolle.[1] This subject was not, however, definitely investigated.

The statements of Friedberger, Ishioka, and of Busson, in regard to pneumonic changes in the lungs of sprayed animals were, to a degree, confirmed. Such lungs as autopsy frequently revealed air-free hemorrhagic areas of limited extent. The affected portions when removed would sink in water, but they were soft and not resistant as in pneumonic consolidation. This postmortem change was by no means constant among sprayed pigs and was also found in animals dying from toxic injections, which had not been sprayed at all.

Possible Atrophy of the Olfactory Epithelium. Because of its importance I venture mention of a theme on which investigation was started but abandoned early in this work. In animals deprived of their olfactory lobes and even in some under other and functional, experimental conditions, there seemed to be a well-marked atrophy of the olfactory mucous membrane as disclosed by cutting away the roof of the nasal cavities. The subject was pursued no further than to give a basis for special research.

[1] Ann. d. l'Inst. Pasteur, 1907, xxi, 128.

The Effect on Tuberculous Guinea-pigs of Tuberculin Applied to the Peripheral Epithelium. It was, of course, a surface thought that some useful therapeutic purpose might be served by treating a systemic affection through the peripheral epithelium. Tuberculous guinea-pigs were the subjects and the old tuberculin of Koch was the remedy. Six young guinea-pigs were inoculated with what proved to be a very attenuated culture of tubercle bacilli, kindly furnished me by Dr. G. B. Webb, of Colorado Springs, on July 25. Three of the animals were inoculated in the peritoneum and three beneath the skin. Two were used as controls and four were treated. The treatment consisted in dropping into the mouth of two subjects in a way to excite the maximum taste sensations, or instilling into the nose (two subjects) dilutions of old tuberculin usually of 0.5 to 1 per cent. strength. Treatment was given every day to every fourth day. Treatments were begun more than six weeks before the inoculations and were continued for more than two months afterward. Superficial observation could detect no particular reaction to the treatments except the excitement of slight dyspnea with spraying (which was practised later). One of the treated pigs had to be killed October 23 because of a tuberculous swelling occluding the urethra. The other pigs all gained in weight and were sacrificed for specific purposes, nearly four months after their inoculation with tubercle bacilli. Postmortem examination left no manner of doubt as to the effect of treatment: The extent and intensity of the tuberculous processes were much greater in the treated animals than in the controls.

Discussion and Summary. Certain of the facts recorded seem to furnish evidence which must be considered in further discussions of the old problem of the physiological requirements in ventilation. The trend of opinion has lately been to ascribe the deleterious properties of rebreathed air solely to the untoward physical conditions of heat and humidity usually involved. Rosenau and Amoss[1] recently published experiments tending back to the old "chemical" view of noxiousness of rebreathed air. Their work has been controverted in literature not available to me.

[1] Jour. Med. Res., 1911, xxv, 35.

The observations, detailed above, on the desensitization of guinea-pigs when exposed to the smell of horses seem to establish beyond question, if such proof were needed, that animal effluvia when inhaled can produce, and at once, profound systemic disturbance. It is usually taken for granted that "ventilation" has the same biological import for all people. On the contrary, it may well be that people suffering from various ailments may find in rebreathed air noxal elements specifically related to their infections (as did my guinea-pigs in the stable). Such a conception, of course, vastly complicates the biological consideration of ventilation. For many years I have noticed in carrying out physical examination on the sick that the subjects of pulmonary tuberculosis appeared especially prone to avoid, as far as possbile, the inhalation of the examiner's breath; it has seemed to me an instinctive effort toward specific self-protection.

Evidence has been brought forward which indicates a peculiar immunological relation between the central nervous system, or at least the brain, and the body. The brain can be sensitized and desensitized an indefinite number of times without essentially changing the susceptibility of the body. (Besredka records three desensitizations in some animals within a few days.) This desensitization of the brain after horse serum injection may be brought about by a number of different agencies;[1] the specific antigen, as used by Besredka, or something allied to it, and contained in the effluvia of horse, or, as I have shown, by cutting the olfactory nerves, lacerating the brain tissue or even setting up of mechanical vibrations in it. Rapid desensitization of the brain is marked by a more or less profound nervous shock following which there is a brief period of anti-anaphylaxis during which the animal is absolutely protected from the poisonous antigen. The nerve impulses producing this remarkable somatic change must operate on the living tissues. It appears probable that these nerve impulses cause the tissues, as it were, to open their receptors for the specific antibody in the blood.

If this "allergin" is removed from the circulation an animal has become essentially normal as regards reactivity to that antigen.

[1] Cf. Kolle and Wassermann, Op. cit., p. 1086.

Fixed in the tissues the allergin combines with more or less antigen contained therein and we witness a degree of shock proportional thereto. It is significant that all observers seem to agree that the allergin diminishes greatly or disappears from the circulation during the phase of anti-anaphylaxis.[1] According to the conception presented here the allergin gets loose from the tissues after a longer or shorter interval and, returning to the circulation, susceptibility to the antigen is resumed.

The widely accepted view of Friedberger[2] that anti-anaphylaxis depends upon the saturation of the anaphylactic antibody with the newly introduced antigen cannot explain the state when caused by brain mutilation; nor does the conception of this author of the two states of non-specific and specific anti-anaphylaxis clear the matter. In fact, Bessau[3] makes a strong stand against Friedberger's theory and concludes that anti-anaphylaxis results from a reaction of the organism through which its irritability is depressed as regards the anaphylactic poison. Evidence has been developed to show that the irritability of the brain, using this term in a broad physiological sense, is to an extraordinary extent dependent upon olfactory stimuli. The teleological interpretation of these coördinations is irresistible. An animal smells many agents to which his body is sensitized and which, if eaten, would act as poisons *per se*, but through the olfactory sense the brain is sufficiently stimulated by the odor of the antigen to discharge impulses which set up in the body a state of anti-anaphylaxis during which the intrinsically poisonous substance may be ingested with impunity. The reaction of my guinea-pigs in the stable give substantial support to such a conception. The possible relations of these conceptions to human physiology, psychology, and surgery are obvious. The experiments with local applications of serum to the nose or by inhalation of a spray show clearly that sensitization of the respiratory epithelium develops after a definite latent period whose length does not appear to be influenced by previous general sensitization of the body.

[1] Cf. Valuable paper by Anderson and Frost, Hygienic Laboratory Bull., 64, Washington, 1910.
[2] Zeitschr. f. Immunitätsf., 1909, ii, 208.
[3] Centralbl. f. Bakt. u. Parasitenk, 1911, lx, 637.

In the masterly and lucid monograph[1] of the Vaughans it is held that the important factor determining the refractory state of the re-injected animal "is the changed relation between the amount of ferment and the substrate." That is, the small amount of antibody remaining in the blood of the anti-anaphylactic animal becomes functionally inoperative in the presence of a great excess of antigen. This view, also, fails to account for the facts I have detailed.

In contrast to this relative independence of central and peripheral sensitizations, it is found that sensitization of the nasal respiratory tract involves the pulmonary epithelium, and *vice versa*, though each reacts with its own "local sign."

The local reactions of the animal inevitably suggest that local anaphylaxis is a state of active resistance against absorption of the antigen. Transferring this idea to bacterial focal infections in the interior of the body we get a more reasonable explanation of the beneficial results which often follow the injection of antiginous bacterial bodies which can come into intimate contact with tissues capable of antibody formation. Finally, the proof is once more absolute that serum dropped in the nose or given by inhalation sensitizes the body, and irrespective of the olfactory apparatus.

The obvious explanation of the fact is that the antigen is absorbed by the circulation, as is supposed to be the case when serum is introduced into the rectum.[2] But "obvious explanations" are especially dangerous.

Unfortunately, I have not been able to show that such peripheral application of the antigen in any way influence the reactions of a subcutaneously sensitized animal to the toxic intravenous injection. This seems a surprising fact in view of the accepted teaching that repeated injections of sublethal doses of serum produce a resistance if not full immunity in an animal. That some peculiar status is occupied by the phenomena induced by application of serum to the respiratory epithelium seems shown by the fact that in two cases unsensitized guinea-pigs, from one of which the olfactory lobes had been removed, were somatically sensitized by this means and that

[1] V. E. Vaughan, V. C. Vaughan, Jr., and J. W. Vaughan. Protein Split Products, 1913, p. 312.

[2] Vaughan, Op. cit., 259.

they thereafter withstood several toxic injections separated by intervals of about two weeks. Experimental analogies have been presented for the anaphylactic phenomena of hay fever and bronchial asthma. It is shown that both a general and a local sensitization are to be considered, interdependent but each having an autonomy.

Briefly summarized, the following conclusions may be drawn:

Guinea-pigs sensitized to horse serum may be desensitized by residence in a horse stable. It is probable that this reaction may be rapidly achieved through the olfactory sense or more slowly by absorption through the respiratory mucous membrane. The period of antianaphylaxis is of less than two days' duration. The converse of this, sensitization of normal guinea-pigs in stable air, I have not been able to achieve.

Removal of part of the brain of a sensitized guinea-pig produces much more severe shock than the same amount of injury in a normal animal. This shock is apt to be followed by a period of anti-anaphylaxis of short duration.

Section of the olfactory nerves within the cranial cavity preceding the brain operation by a day or more abolishes the tendency to shock. Such nerve section in the normal animal also seems to reduce the shock arising from definite brain injury.

Depression of the olfactory sense through cocaine and the resemblance of symptoms from poisoning with this drug to those of anaphylaxis are discussed.

The body as a whole may be sensitized through the peripheral application of horse serum after a definite latent period which does not seem to be affected by previous general sensitization. A normal animal, so treated, may resist large intravenous injections of serum repeated at intervals of two weeks.

Sensitization of one area of the respiratory epithelium involves sensitization of the rest, though the local signs of expression are different.

The evidence indicates that local anaphylaxis, induced through the periphery, precedes the development of general sensitization.

Tuberculous guinea-pigs were made worse when treated by instillations or sprays of old tuberculin.

Besides the expression already made regarding Dr. Powell, it is a pleasure to acknowledge my indebtedness to my colleagues Dr. W. C. Mitchell and Dr. Ph. Hillkowitz, for many favors, and to Dr. Auer, of the Rockefeller Institute, for hints as to technique.

A COMPARISON OF THE RESULTS OF THE PHENOLSULPHONEPHTHALEIN TEST OF RENAL FUNCTION WITH THE ANATOMICAL CHANGES OBSERVED IN THE KIDNEYS AT NECROPSY

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Among the most important questions that come before the physician are the ever-recurring inquiries: Are the kidneys the seat of chronic disease, and, if so, how extensive is the process? What is the outlook?

For the past four years we have used the phenolsulphonephthalein test of Rowntree and Geraghty in a considerable variety of conditions in the medical wards of the Johns Hopkins Hospital, and as a result of our observations we have come to regard the procedure as one of considerable value both in the diagnosis and prognosis of renal disease.

Most of the results which have been reported by those who have made use of this method have been based upon clinical observations alone. Occasional necropsies have been described, but nowhere, so far as we are aware, has there appeared any large series of consecutive clinical observations followed by necropsy.

Here and there there are reports, on the one hand, of great variations in the test made from time to time in individual cases, and on the other hand of instances where an approximately normal or even high excretion of 'phthalein has been observed in patients who have died shortly and unexpectedly thereafter with all the signs of an

uræmia. In some of these instances, notably the cases reported by Foster, necropsy has revealed what was regarded as extensive chronic renal change.

It seemed to us, therefore, that further light might be thrown upon the situation by a consideration of those fatal cases occurring in the medical service of the Johns Hopkins Hospital in which, after the 'phthalein test had been made during life, a necropsy with careful microscopical study of the kidneys has followed. The fact that many of these cases were presented at the Clinical and Pathological Conference, where a definite opinion was expressed by the clinician as to the nature of the case before he was aware of the results of the necropsy, has added considerably to the interest of the work.

Dr. Winternitz, who has for some years been engaged in the study of the pathological anatomy of nephritis, has been so good as to go over all the specimens and to express his conception of the anatomical nature of the process without previous information concerning the clinical history of the case. An anatomical classification of the material was thus made from a purely objective standpoint. The clinical histories of the patients were then thoroughly analyzed and the results of our functional tests were considered in their relations to the anatomical changes in the kidneys and to the conditions existing at the time when the tests were made.

There were fifty-four cases followed by necropsy in which the 'phthalein test was made during life. The material was classified anatomically as follows:

Advanced chronic nephritis	20 instances
Chronic nephritis of moderate extent	6 instances
Cloudy swelling in association with grave acute infections	6 instances
Severe acute nephritis	1 instance
Amyloid kidney	1 instance
Hypernephroma (unilateral)	1 instance
Chronic passive congestion (cardiac disease)	20 instances

Advanced Chronic Nephritis. The anatomical changes here observed were those of a progressive chronic inflammatory nephritis with more or less granular atrophy in gross, and microscopically, adhesive glomerulitis, hyaline glomeruli, a greater or less amount of interstitial change—infiltration, œdema, scarring. Acute terminal

changes—hæmorrhages, exudate, cellular infiltration, epithelial swelling, and degeneration—varied in extent.

In these 20 patients, as may be seen in the accompanying table (Table I), 33 estimates of the 'phthalein output were made, the figures varying from 0 to 38 per cent. in two hours.

Table I.—Advanced Chronic Nephritis.

No. of cases.	Period before death.	Percentage of 'phthalein in two hours.
3	10 days	7.0 per cent.
3	9 days	3.1 per cent.
8	12 days	trace
11	5 days	0
18	7 days	18.0 per cent.
21	8 months	24.0 per cent.
21	57 days	35.0 per cent.
21	41 days	36.0 per cent.
21	23 days	34.0 per cent.
21	18 days	16.0 per cent.
23	4 months	10.0 per cent.
23	28 days	trace
24	105 days	20.0 per cent.
24	72 days	trace
24	62 days	trace
27	6 days	37.0 per cent.
29	14 days	7.0 per cent.
31	3 months	18+ per cent.
33	4 days	0
38	3 days	0 (1 hour)
39	3 days	38.0 per cent.
II.	6 days	15.0 per cent.
III.	5 days	0
IV.	3 weeks	6.9 per cent.
IV.	13 days	16.6 per cent.
VI.	23 days	trace
VI.	2 days	13.0 per cent. 1 hour
X.	40 days	26.0 per cent.
X.	31 days	trace
X.	30 days	trace
X.	day of death	trace
XV.	4 days	slight trace
XVI.	43 days	1.5 per cent.

The test was made *within a week before death* in 11 cases, the excretion in two hours varying from 0 to 38 per cent. The percentage of 'phthalein output was as a rule very low—under 18 per cent. The two instances (Cases 27 and 39) with a higher excretion were patients who died respectively of a dissecting aneurysm and a hemiplegia, accidents coming on in the course of a nephritis which had not as yet reached a stage of decompensation.

The test was made *within a month, and over a week before death* in 7 patients. Here the excretion of 'phthalein in two hours varied

from a trace to 34 per cent. Patient 21, in whom the excretion was highest, namely, 34 per cent., twenty-three days before death, was an instance of chronic nephritis in a woman of sixty-four with great cardiac insufficiency which unquestionably hastened death. Other functional tests made in this patient showed, also, more favorable results than has been the rule in instances in which the terminal stage of the nephritis has been reached without the intervention of cardiac failure. The test was made at periods from *one to eight months before death* in 5 patients, the excretion varying from 1.5 per cent. to 35 per cent.; it was above 20 per cent. only in Case 21—the patient with cardiac insufficiency above referred to.

Among all these patients records above 36 per cent, were obtained in but three instances—Cases 21, 27, and 39. Two of these records, each in the thirties, were obtained in the patients dying respectively from a dissecting aneurysm and hemiplegia. The third instance was the case of myocardial insufficiency above referred to where death was associated with hydrothorax and extensive dropsical manifestations. Here also the excretion of 'phthalein fell to 16 per cent. eighteen days before death.

In these patients the renal changes had not presumably reached a stage at which decompensation and uræmia were imminent.

The *manner of death* in these 20 cases was from uræmia in every instance with the exception of Patients 27 and 39—who died suddenly from the rupture of a dissecting aneurysm and hemiplegia respectively. In Case XVI there was a terminal meningitis, but this had been preceded by unquestionable uræmic manifestations.

In almost all patients there was cardiac hypertrophy of greater or less extent, but in only three was death in any direct sense due to cardiac failure (Cases 21, 31, and VI).

The *urine* in all of these instances was of low specific gravity, and toward the end scanty although there was generally a history of preceding polyuria. Albumin was present generally in a moderate quantity. In several cases the albumin was abundant at the end in association with ischuria and acute terminal changes. The sediment was, as a rule, scanty, consisting of hyaline and granular casts and occasional red blood corpuscles. In two instances (Cases 23 and 24) where there was anatomically more epithelial change, epi-

thelial casts were also found in the urine. In but two instances (Case 29, the hemiplegic, and case IV) was the specific gravity at all high. Case IV was an instance with rather rapid clinical course and a good many acute anatomical changes. Here also there were, toward the end, numerous hyaline, epithelial, and blood casts.

The *maximum blood pressure*, as shown by the following table, was elevated in almost every instance.

Blood Pressures.

Case 3	95
Case 8	235
Case 11	140 to 175
Case 18	180 to 205
Case 21	240
Case 23	130 to 153
Case 24	216
Case 27	170 to 180
Case 29	130 to 140
Case 31	225
Case 33	167 to 138
Case 38	188
Case 39	200 to 80
Case II.	226 to 236
Case III.	230 to 80
Case IV.	115 to 175
Case VI.	180 to 260
Case X.	180 to 220
Case XV.	170 to 220
Case XVI.	142 to 160

The one instance (Case 3) in which the blood pressure was low is worthy of special note. The patient, a boy of twelve, was admitted to the hospital complaining of polydipsia and polyuria of several years' duration. For two years he had suffered from pains in his legs, rather sharp in character and interfering with his walking; probably from his description, muscular cramps. The physical examination showed a pale boy with rather dry skin and no demonstrable cardiac hypertrophy. The radial arteries were, however, palpable; the maximum blood pressure was 95; the eye-grounds showed no changes. The urine on entry amounted to about 2500 c.c. in twenty-four hours; specific gravity, about 1005; no albumin; no formed elements in the sediment. The 'phthalein test a week after entry, showed a total excretion in two hours of but 7 per cent., and on the following day but 3.1 per cent. Within a day or two the quantity of urine began to diminish, a trace of

albumin appeared, and occasional hyaline and granular casts were found in the sediment. The boy became dull and drowsy and, nine days after the last 'phthalein test, died in uræmic coma.

At necropsy the kidneys were found to be exceedingly small and granular, the cortex greatly thinned. On microscopical examination there was little cortical substance left, most of the glomeruli being completely degenerated and represented by small hyaline masses. This is the most striking instance that we have had of the value of the 'phthalein test. Without it we might well have failed to recognize the nature of the case.

Further Tests of the Renal Function. In 9 of these instances further tests of renal function were made. The incoagulable N. in the blood was estimated fifteen times in 7 patients.

In six tests made in 5 patients *within a week before death* the incoagulable N. was:

Case 21	0.5	grammes per litre.
Case 23	1.8	" "
Case X.	1.876	" "
Case 23	2.0	" "
Case 33	2.0	" "
Case 18	2.1	" "

In nine tests made in 5 patients *at longer periods before death* the incoagulable N. was:

Case 21	8 months	0.4	grammes per litre.
Case 21	52 days	0.48	" "
Case 21	40 days	0.43	" "
Case X.	14 months	0.9	" "
Case X.	31 days	0.84	" "
Case X.	30 days	0.864	" "
Case 31	65 days	1.0	" "
Case 23	28 days	0.88	" "
Case VI.	23 days	0.63	" "

The two instances (21 and VI) in which rather low figures were obtained were both cases in which there were grave cardiac complications and chronic passive congestion, instances in which, although the renal changes were grave, it is yet very possible that they had not reached an extent sufficient of itself to have induced uræmia.

The *lactose* elimination was suppressed or greatly delayed and diminished in all the 9 cases in which it was tested.

The *chlorides* were studied in 6 patients. In three (11, 31, and VI) the elimination was rapid and complete with polyuria (vascular hyposthenuria). The test was made respectively five, sixty-five, and twenty-three days before death.

In 3 cases (18, 27, and XV) one week, seventy-five days, and four days respectively before death the *chlorides* were in part retained. In the first case there was tuberculous pleurisy and peritonitis; in the second, at the time of the test, there was general anasarca and ascites; in the third, an instance of very marked renal change, there was slight œdema.

Iodide of potassium was eliminated in forty-eight hours or less in Cases 18 and VI. It was delayed in Cases 11 (seventy-two hours), 21 (fifty-four hours), 31 (seventy-two hours) and XV (seventy-two hours).

Relation of the Percentage of 'Phthalein Excreted to the Length of Survival. The percentage of 'phthalein excreted in two hours was 20 or over in 9 tests (6 cases); longest survival, eight months.

The percentage of 'phthalein was from 10 to 20 in six tests (6 cases); longest survival, four months.

The percentage of 'phthalein excreted in two hours was under 10 in sixteen tests (12 cases); longest survival, seventy-two days.

The percentage of 'phthalein was a trace only in seven tests (4 cases); longest survival, seventy-two days.

The 'phthalein was wholly suppressed in four tests (4 cases); longest survival, five days.

These results are quite in accord with those with which we have met in this clinic in the past four or five years in cases which have not come to necropsy. In no instance of grave chronic nephritis have we failed to find a material diminution in the 'phthalein excretion. In not a single instance in all the studies made at this clinic by Rowntree, Geraghty, Mrs. Winternitz, Fitz, Baetjer, and Snowden have we met with an instance such as those reported by Foster, in which an excretion approaching normal was found in grave chronic nephritis shortly before death. The study of these cases in which we have been able to make the anatomical control, tends to support our previous impression that the test is one of considerable diag-

nostic value. This study further reveals in rather a striking manner the progressive diminution of the 'phthalein excretion with the advance of the disease. This is so definite as to give the test a considerable prognostic significance.

The anatomical observations suggest that in a good many instances the terminal event, which was almost invariably uræmia, was ushered in by acute renal changes which did not manifest themselves by any striking alterations in the urine. In many of these instances, a few days before death or at the onset of uræmia, the 'phthalein was excreted in but a trace. It is not impossible, however, that a month previously the percentage might have been considerably higher—20 per cent. or even more. Nevertheless, we are considerably impressed with the consistency with which a low 'phthalein output is found in chronic nephritis of any essential degree, and we feel that in the absence of chronic passive congestion the 'phthalein test gives us important diagnostic and prognostic help.

Chronic Nephritis of Moderate Extent. There were 6 cases of chronic nephritis of moderate extent. Of these 5 (Cases 4, 13, 17, 20, and XIV) were associated with a high degree of chronic passive congestion due to cardiac failure. The other (Case 13) was an instance of tuberculous polyserositis with a considerable degree of cardiac insufficiency.

The renal changes in these patients were not extensive, a few glomerulo-capsular adhesions, but little scarring, some exudate with red blood corpuscles in the glomerular spaces. The kidneys showed little gross deformity. In Case XIV, an instance of verrucose endocarditis, the changes were however, more marked and acute than in the others.

The *urine* in all instances was scanty, the specific gravity, however, tended to be rather below normal, excepting in Case XIV, where it ranged from 1020 to 1026. The albumin varied from a trace to a considerable amount. In Case 17, an instance of dilated heart with grave passive congestion and acute endocarditis, the albumin at the end was 0.9 per cent.

The 'phthalein output in two hours, as shown by Table II, varied from 16 to 42 per cent.

TABLE II.—Chronic Nephritis of Moderate Extent.

No. of cases.	Period before death.	Percentage of 'phthalein in two hours.
4	9 days	39.5 per cent.
13	7 months	22.0 per cent. (3 hours)
13	5½ months	32.0 per cent.
17	32 days	23.0 per cent.
20	12 days	42.0 per cent. (3 hours)
IX.	18 months	36.0 per cent.
XIV.	1 day	16.0 per cent.

The test was made *within a week of death* in but one instance when, on the day before death, it was 16 per cent.

The test was made *between one and two weeks before death* in 2 instances, when it was respectively 39.5 and 42 per cent. in three hours.

In Case 13, an instance of tuberculous polyserositis with cardiac failure, the output seven months before death was 22 per cent. in three hours, and 32 per cent. in two hours one month and a half later when the patient was in an improved condition.

The *chlorides* at the time of the first test were well excreted; the lactose was excreted in twelve hours; urea, 0.6 grammes per litre; catalase, from 14.2 to 31.

In Case 20, twelve days before death, the lactose was excreted in eleven hours; K.I. in sixty-two hours, while the incoagulable N. was 0.5 per litre of blood.

In Case IX, eighteen months before death, with a 'phthalein of 36 per cent., the lactose excretion was much delayed and the urea in the blood was 0.8 grammes per litre.

The *blood pressure* in this series, as will be seen by the following table, was not strikingly high, owing possibly to the condition of the heart.

BLOOD PRESSURES.

Case 4	125 to 160
Case 13	140 to 210
Case 17	190
Case 20	90 to 110
Case IX.	110 to 140
Case XIV.	112 to 130

On the whole, this group represents older individuals than those in whom more advanced nephritis was found, individuals whose weakened hearts have been less able to resist the hypertension of a

developing nephritis. Death, therefore, has occurred from circulatory failure at an earlier period of the renal disease. The analysis of the ages of these 6 patients shows that with one exception they were all over 40, the average age amounting to 47+, while the average age of the 20 patients with advanced chronic nephritis was but 38.8, despite the fact that one patient aged 71 is included in this list.

Cloudy Swelling. There were five instances of cloudy swelling occurring during severe infections. The nature of the infection was:

Pneumonia and gangrene	Case 1
Acute endocarditis	Case 2
Osteo-myelitis and abscess of the knee	Case 6
Syphilis, bed-sore, bronchopneumonia and gangrene	Case 7
Miliary tuberculosis	Case 34

The microscopical changes in the kidneys were not extensive—swelling and granular degeneration of the epithelium, engorgement of the capillaries with the occasional escape of a few red blood corpuscles into glomerular space or tubules.

The percentage of 'phthalein excreted in two hours varied, as may be seen from Table III, from 20 per cent. on the day of death (Case 2) to 50 per cent. forty-five days before death (Case 6).

Table III.—Cloudy Swelling.

No. of case.	Period before death.	Percentage of 'phthalein in two hours
1	9 days	27.0 per cent.
2	day of death	20.0 per cent.
6	6 months	37.8 per cent.
6	10 days later	29.7 per cent.
6	45 days	50.0 per cent.
7	20 days	33.0 per cent. (5 hours)
34	9 days	28.0 per cent.

The test was made *within two weeks before death* in three instances (Cases 1, 2, and 34), the 'phthalein excretion varying from 20 to 29 per cent. In Case 2, in which the output was but 20 per cent. on the day of death, the actual renal changes were not more marked than in the other instances but there was grave chronic passive congestion. In Case 34 the epithelial degeneration was more extensive than in any other case in this group and the 'phthalein output nine days before death was 28 per cent.

The test was made at a period *from twenty days to several months*

before death in 2 instances, the 'phthalein excretion varying from 33 per cent. in five hours to 50 per cent. In the former instance, however, the test is of little value, owing to the long period of time over which it was made and to considerable uncertainty which existed as the proper saving of the specimens. The variations in the records of Case 6 are interesting. The patient suffering from abscess of the knee and osteo-myelitis was febrile at the time of the first two tests (37.8 and 29.7 per cent.). At the time of the third test (50 per cent.) he was afebrile and in a much better general condition.

In all of these cases the *urine* was rather scanty, of normal or high specific gravity, the albumin varying from a trace, with a few hyaline and granular casts in the sediment, to a large amount with hyaline, granular, epithelial, and blood casts (Case 2, acute endocarditis). Excepting in Case 2, where there was grave cardiac insufficiency, and in Case 34, acute miliary tuberculosis, anasarca was absent or an unimportant factor.

Our *clinical diagnosis* as to the renal condition was "cloudy swelling" in Cases 1, 6, and 7; in Case 2, "chronic nephritis with an acute exacerbation;" while in Case 34 a diagnosis was not recorded before the result of the necropsy was known.

In one instance not included in this list there was widespread epithelial necrosis (Case 5). This was a case of syphilis of the aorta with valvular insufficiency, extreme cardiac dilatation and chronic passive congestion. There was a terminal peritonitis and colitis. The 'phthalein test, however, was made nearly a month before death and was interesting only for its association with chronic passive congestion, in which group the case is classified.

As we consider these figures then it is clear that a terminal cloudy swelling may be associated with considerable diminution in the 'phthalein output.

Severe Acute Nephritis. There was one instance (Case 10) of severe acute nephritis, a man of forty-eight, with ulcerative endocarditis and general septicæmia with a pneumo-streptococcus; anæmia; purpura; pulmonary, splenic, and renal infarcts; terminal broncho-pneumonia, pleurisy; and death in coma. The *blood pressure* was 135.

The *kidneys* were large; the cortex swollen; the parenchyma pale.

Microscopically there was evidence of a grave acute nephritis with much œdema, catarrhal and exudative glomerulitis, and extensive epithelial degeneration.

The 'phthalein excretion four days before death was but a trace in four hours and the urea in the blood was 1.2 grammes per litre.

Amyloid Kidney. There was one instance of pure amyloidosis, a woman of thirty-three with an old syphilis, complaining of dyspnœa on exertion for five months and swelling of the extremities for a month. She was very anæmic. The *blood pressure* was rather low, ranging from 92 to 124.

The *urine* was very scanty, showing from 0.4 to 1 per cent. of albumin and a specific gravity of from 1012 to 1015, with occasional hyaline casts. Two days before death the patient became stuporous and comatose.

Ten days before death the excretion of 'phthalein in two hours was but 1.2 per cent.; *two days before death* but a trace was observed.

The kidneys at autopsy showed characteristic amyloid disease with extensive glomerular change and slight interstitial fibrosis.

Hypernephroma. In Case 30 a large irregular tumor was palpable in the right renal region. The ureters were catheterized, and from the right side no 'phthalein was obtained; from the left, 17 per cent. was excreted in fifteen minutes. The left kidney was found to be hypertrophied; the right was almost entirely destroyed, consisting largely of neoplastic tissue.

Chronic Passive Congestion. There were 20 instances in which the kidneys anatomically showed changes suggesting only chronic passive congestion. Clinically these were all cases of cardiac dilatation and insufficiency.

The main lesion in each of these cases was:

Fibrous myocarditis	8 cases	(Cases 9, 12, 16, 22, 32, 36, V, VIII)
Syphilis of the aorta	7 cases	(Cases 5, 10, 14, 25, 26, 37, VII)
General arteriosclerosis	2 cases	(Cases 19, 35)
Emphysema and pulmonary induration	2 cases	(Cases XI, XII)
Adherent pericardium	1 case	(Case XIII)

As may be seen by Table IV, the excretion of 'phthalein in two hours varied very greatly according to the degree of cardiac compensation, ranging from a trace to 71 per cent.

TABLE IV.—Chronic Passive Congestion.

No. of cases.	Period before death.	Percentage of 'phthalein in two hours.
5	29 days	28.2 per cent.
9	6 months	25.6 per cent.
9	68 days	58.6 per cent.
9	10 days	59.0 per cent.
10	13 days	30.5 per cent.
10	3 days	25.4 per cent.
12 (active diuresis)	4 months	72.0 per cent. (3 hrs. 50 m.)
14	20 weeks	37.0 per cent.
14	12 weeks	22.0 per cent.
16	40 days	48.0 per cent. (3 hours)
19	93 days	50.0 per cent.
22	14 days	31.0 per cent.
25	11 weeks	71.0 per cent.
25	3 days	55.0 per cent.
26	4 months	24.0 per cent.
26	7 days later	63.0 per cent.
32	38 days	48.0 per cent.
35	3 days	28.3 per cent.
36	35 days	trace
36	29 days	38.0 per cent.
36	1 day	trace
37	5 days	69.0 per cent. (2½ hours)
V	1 day	16.1 per cent.
VII	6 months	16.0 per cent.
VII	1 week later	36.0 per cent.
VII	1 week later	45.0 per cent.
VIII	1 year	50.0 per cent.
VIII	8½ months	39.0 per cent.
VIII	12 days	54.0 per cent.
XI	3 days	45.0 per cent.
XII	3 months	49.0 per cent.
XIII	2 months	61.0 per cent.

In nine cases the percentage of 'phthalein excreted in two hours was under 30 per cent. (Cases 5, 9, 10, 14, 26, 35, 36, V, VII). In all of these instances there was grave cardiac decompensation. The nature of the change was as follows: In 4 cases (5, 10, 14, 26) syphilis of the aorta with aortic insufficiency and its sequels.

In 4 cases (9, 35, 36, VII) fibrous myocarditis with dilatation.

In 1 case (V) a fibrous myocarditis associated with chronic endocarditis and mitral insufficiency.

Cases 9, 26, 36, and VII are especially interesting as showing what remarkable variations may occur in one individual under varying circumstances. Thus in Case 9, a colored woman with great cardiac dilatation, the output during a period of decompensation six months before death was 25.6 per cent. Under rest and diuretics there was great improvement, and death came on suddenly while the

patient was apparently in fair condition. Twice later, when compensation was reasonably good, sixty-eight and ten days before death respectively, the 'phthalein output was 58.6 and 59 per cent.

In Case 26, a colored man with syphilitic aortitis and aortic insufficiency, the 'phthalein, during a period of decompensation, was 24 per cent.; a week later in compensation it was 63 per cent.

In Case 36, a colored man with fibrous myocarditis and chronic mitral disease while in a condition of grave decompensation five weeks before his death, at a time when the urine was very scanty and showed a trace of albumin and hyaline and granular casts, the 'phthalein output was but a trace. A week later the patient was much better and, although he was still œdematous, the output of urine was above the intake. The 'phthalein excretion was 38 per cent. One day before death when the urine again was very scanty the output of 'phthalein was but a trace.

In Case VII, a man of 61 with myocarditis and dilated heart, the output of 'phthalein six months before death during a period of decompensation was 16 per cent. A week later, when he was improving, it was 36 per cent. Yet a week later it was 48 per cent.

The *urine* in these instances of chronic passive congestion was scanty, the specific gravity normal or increased. There was a trace of albumin and a few casts, excepting in Case 10, where toward the end, in association with a terminal infection, there was from 0.6 to 0.7 per cent. of albumin and numerous hyaline, granular, and epithelial casts. Anatomically, in this instance, there was extensive acute epithelial necrosis, but no 'phthalein test was made at the periods when this must have occurred.

The *blood pressure* in these patients, most of whom showed cardiac hypertrophy as well as dilatation, may be seen in the accompanying table.

The figures for our instances of chronic passive congestion show then, in general, a moderate diminution in the amount of 'phthalein excreted in two hours, a diminution which, in some cases, may be extreme, amounting almost to complete suppression. This is wholly in accord with the experiments of Rowntree and Fitz.

Blood Pressures.

Case 5	160 to 187
Case 9	170 to 210
Case 10	135
Case 12	100 to 122
Case 14	120 to 130
Case 16	82 to 124
Case 19	200
Case 22	175 to 210
Case 25	95 to 124
Case 26	120 to 160
Case 32	180 to 182
Case 35	202 to 242
Case 36	130 to 175
Case 37	150 to 175
Case V	112 to 150
Case VII	135 to 150
Case VIII	125 to 190
Case XI	135
Case XII	110
Case XIII	100 to 115

In 9 cases (14, 16, 19, 22, 25, 26, VII, VIII, XI) other tests of renal function were carried out, as may be seen in the following table:

Table V.—Showing Various Tests of Renal Function in Cases of Chronic Passive Congestion.

No. of cases.	'phthalein excretion in two hours.	KI.	Lactose.	Chlorides.	Grammes of incoagulable N. per litre of blood.	Grammes of urea per litre of blood.
14	37 per cent.	68 hours.	9 hours.	Retained	0.49	
16	48 per cent.	72 hours.	19 hours.			
19	50 per cent.	56 hours.	10 hours.	Retained	0.21	
19	A week later, improved; polyurea.			Good excretion		
22	35 per cent.	62 hours.	10 hours.	....	0.4	
22	3 days later.	..	....	....	0.36	
25	71 per cent.	80 hours.	9 hours.	Retained	0.192	
25	55 per cent.	..	12+ hours.	....	0.47	
26	24 per cent.	48 hours.	Trace only in 1 hour.	....	0.33	
26	63 per cent.	..	4 hours (normal amount)			
VII	16 per cent.	..	....	Poor excretion		
VIII	54 per cent.	48 hours.	50 per cent. in 3 hours.	Good excretion		
VIII	Later	..	Trace only in 5 hours.	Good excretion	....	0.5
XIII	61 per cent.	..	Trace only in 4 hours.	....	0.4	

These tests show the variability of the results with iodide of potassium, on which we have learned to place little reliance. The

lactose excretion is profoundly modified in chronic passive congestion. A striking example of this is to be seen in Case XIII, where the lactose is almost suppressed while the 'phthalein excretion is fairly good.

Although the incoagulable N. or urea was estimated nine times in 7 cases, and during periods of grave decompensation where the 'phthalein excretion was as low as 24 per cent., in no instance was the urea above 0.5 nor the incoagulable N. above 0.49 per litre.

It is clear then that chronic passive congestion alone may result in a very marked reduction in the 'phthalein output in the first two hours, a reduction which in extreme instances may amount almost to suppression. With the return of compensation, however, the excretion of 'phthalein rapidly regains the normal precentage.

The incoagulable N. in the blood has not been high in any of our cases even at times when the elimination of 'phthalein has been considerably interfered with.

Summary and Conclusions. These observations show, in severe chronic nephritis, a uniformly low 'phthalein output which, as a rule, in those instances not interrupted by an acute terminal process, decreases steadily up to the onset of uræmia, and is nearly or wholly suppressed from a day or two to a month before death. Acute terminal processes which may be unsuspected clinically, are common, and here a sudden diminution in the elimination of 'phthalein may come on in cases where the percentage previously excreted is not so low as to appear menacing.

In not a single instance, and indeed not once in all the studies of the last five years, have we met with a case of severe chronic nephritis[1] with a good 'phthalein elimination.

Chronic passive congestion (cardiac disease) results often in a considerable reduction in the two hours' elimination of 'phthalein. The results are very variable in individual cases. In marked decom-

[1] As has been pointed out by Pepper and Austin, and Baetjer there is a stage or form of nephritis in which the excretion of 'phthalein is not interfered with. These instances are more or less characteristic in their clinical manifestations and are often roughly classed as "chronic parenchymatous nephritis." Their most striking clinical features are the elective impermeability of the kidney to salt and the resulting tendency to hydrops. With regard to most other tests of function the kidneys appear to react normally, and beyond the dropsy there are sometimes few disturbing symptoms. These are presumably cases with little glomerular involvement. No such instance has come to necropsy in this clinic.

pensation the 'phthalein output may be reduced to but a trace in two hours; but the excretion is, as a rule, rapidly restored with the reëstablishment of circulatory compensation.

These observations are in agreement with the experimental studies of Rowntree and Fitz.

In the few instances of chronic nephritis of moderate extent which are included among our cases the excretion of 'phthalein was uniformly considerably reduced. All of these cases, however, were associated with chronic passive congestion of considerable extent, but the percentage of 'phthalein was lower than might have been expected with an uncomplicated passive congestion.

In one instance of acute nephritis and in one instance of pure amyloid disease the 'phthalein excretion was greatly reduced.

The cloudy swelling observed in acute infections was in some instances, associated with considerable reduction in the 'phthalein output.

These observations then tend to support our previous impression that the phenolsulphonephthalein test of Rowntree and Geraghty is a procedure of considerable diagnostic and prognostic value, especially in the study of chronic nephritis.

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DISCUSSION

Dr. Charles F. Withington: With regard to the prognostic value of the phthalein test, I will say that we have had in the last three months 20 cases, 5 of which ended fatally. In four of them there was no demonstrable phthalein reaction at the end of two hours. In the fifth case at the end of two hours 10 per cent. of the phthalein was recovered; but that patient had extensive myocarditis, and it is questionable how much the renal trouble had to do with it. No case which showed substantial absence of elimination recovered, and the duration of life after making the test was

in no case longer than two weeks. The other cases showed all the way from 10 to 70 per cent. elimination; in the majority of the chronic cases it was 25 or 30 per cent. One case of pneumonia, where there was only a question of nephritis, showed a recovery of only 25 per cent. phthalein. Cases of bronchitis showed the same. They were discharged without clear evidence of renal trouble. Two surprising cases appeared, one of them an undoubted case of chronic nephritis. The sediment was very abundant in fatty casts. There were from four to half a dozen well-marked fatty casts in each field and yet that man was secreting 62 per cent. of phthalein in two hours. He showed but slight symptoms of his disease and was discharged feeling very well. The functional test here was more indicative of the true gravity of the case than were the findings in the sediment.

One man brought in showed clear evidence of a very acute nephritis, comatose and having had a history of convulsions. Twenty-four hours after he was brought in he showed an output of 70 per cent. phthalein and his condition proceeded to clear up, and he went out feeling "well" two weeks after he was brought in. It was only six or eight days after his coma that he showed this surprising phthalein output.

Dr. Joseph L. Miller: I want to speak of the case of a man who was brought into the hospital unconscious, with a history of convulsions, and all the evidences clinically of uremic coma. As soon as the man recovered from his coma, which was two or three days, and we were able to apply the phthalein test, we found he eliminated in two hours 60 per cent. phthalein. When given the lactose test intravenously, all the lactose was eliminated in two hours. He recovered; went out. Apparently the man had a nephritis and uremic coma.

The other patient was a man who came to the hospital not very ill, in whose case a diagnosis of chronic interstitial nephritis was made; he was passing 2000 c.c. of urine, but we could not get a trace of phthalein through in two hours. In forty-eight hours, up to the time he went into coma, he passed a large amount of urine, and at the end of forty-eight hours, he went into coma and died. Autopsy showed a high degree of interstitial nephritis.

Dr. Thayer (closing): As is mentioned in my full communication, there are of course instances of chronic hydropic nephritis (commonly classified as "chronic parenchymatous nephritis") with few grave subjective symptoms excepting the hydrops. There is generally a large quantity of albumin in the urine, but, as has been pointed out by various observers, the renal function, as studied by most other tests, appears to be practically normal with the exception of the striking tendency toward salt retention.

Two instances especially have interested me during the last several years, one a girl who has been under my observation for a year and a half

and who is subjectively practically well excepting for a frequently recurring dropsy and the inability to excrete chlorides. Under a diet containing only 2 to 3 grams of NaCl she remains in fairly good condition although at present somewhat dropsical, but with the least increase in salt the dropsy becomes marked.

The other instance has been under my observation for about three years, and the history has been almost exactly the same with the exception that the permeability of the kidneys for chlorides has been gradually reëstablished although the albuminuria continues. As Pepper and Austin, and Baetjer have shown, some of these instances show a rather increased permeability with phthalein.

ETIOLOGY OF SOME FORMS OF TROPICAL INFECTIVE GRANULOMATA[1]

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The infectious granulomata may be regarded as new formations of tissue that have resulted from the multiplication of different pathogenic microörganisms, or from the action of their toxins, and which in their structure while possessing some similarity to inflammatory granulation tissue, also show other distinctive features. Macroscopically these new formations often appear as sharply circumscribed nodules, sometimes producing spongy growths or other tumor-like formations, and thus in their external appearance they may resemble the neoplasms or blastomata. In other instances ulcerative processes result about which granulation formations occur. From such characteristics these lesions have been designated in some instances as infectious granulation tumors, in others as infective granulomata. Among the infective granulomata which occur more commonly in certain tropical countries, and which are perhaps of unusual interest from an etiological standpoint, are frambesia, ulcerating granuloma of the pudenda, and verruga peruviana. From observations made during the past summer upon an expedition to South America, the other members of which were Doctors E. E. Tyzzer and A. W. Sellards, and Mr. Charles T. Brues, our knowledge of the cause and nature of verruga peruviana has been greatly elucidated, and it is of this disease I will speak first.

Two definite diseases, verruga peruviana and Oroya fever[2] were

[1] Remarks made in connection with lantern slide demonstration.

[2] A complete report of our investigations concerning these two diseases will be found in the Report of the First Expedition to South America from the Harvard School of Tropical Medicine, 1913, published by the Harvard University Press, Cambridge, Mass., 1914.

formerly generally considered to be merely different stages of the same disease, and hence while the latter complaint is not related to the infectious granulomata, in discussing the previous investigations carried on in regard to verruga peruviana, those relating to Oroya fever necessarily must be considered more or less.

According to the generally accepted opinion the disease verruga peruviana in the severe type begins with an initial stage known as the *fiebre grave de Carrion*, which is characterized by a fever which lasts from fifteen to thirty days, profound anemia, prostration and a high mortality. If the patient does not die in this stage the fever begins to abate, and the eruptive or verruga stage commences. If the eruption is generalized and abundant, then it is stated that the patient is sure to recover. In the chronic or mild type of the disease, which is said to comprise the greater proportion of the cases, there is moderate fever of intermittent or remittent type, and pains in the joints are common; more or less anemia is present. The eruption is said to be the culminating feature in both forms, and it appears under various types, which, according to the special characteristics they reveal, are termed "miliary," "nodular," or "mulaire."

I will now illustrate by photographs the various cutaneous lesions of the disease verruga peruviana. The eruption consists at first of erythematous areas in which groups of small, pinkish papules soon form. Small vesicles also often appear which may be grayish or reddish, or dark blue, according to their degree of vascularity and the character of the blood within them. The areas of skin over which this so-called "miliary" rash appears are frequently edematous, and this is most commonly observed on the legs and more rarely upon the extensor surface of the arms. Unless the disease is arrested the papules grow until they usually measure from 1 to about 5 mm. in diameter. They are usually reddened, raised, and sharply circumscribed from the surrounding tissue, usually discrete, sometimes confluent, and during the most active process of the disease, are of bright or dark cherry color. The skin over them is tense, translucent, and adherent. When injured they bleed freely. Later they assume a gray color or become the color of the skin. To the touch they are usually firm or cushiony. As the disease advances,

in addition to the cutaneous papules deeper subcutaneous nodules appear, which at first may be quite free from the skin and lie deep in the subcutaneous tissue. Later many of these grow toward the surface, and the skin over them becomes involved and adherent. These nodules vary from several millimeters to 3 or 4 centimeters in diameter. The nodular type is especially common about the flexures of the knees and elbows and over the thighs and legs. After these nodules have become adherent to the skin, the skin over them sometimes becomes broken and they may ulcerate, reaching the surface as red, fungating masses. These lesions are known as verrugas of the "mulaire" type and often measure several centimeters in diameter. They also may be pedunculated. While the eruption occurs most commonly on the legs and arms, particularly the extensor surfaces and over the shoulders, it not infrequently appears on the face, forehead, and ears. Sometimes it appears on the trunk. A better idea of its extent and distribution may be obtained from the illustrations. The miliary eruption also may occur upon the mucous membrane of the mouth or nose, or the glans penis. Sometimes when situated in the nose epistaxis may result. After lasting for several weeks and sometimes for three or four months or even longer, during which time the eruption and nodules may disappear and reappear, that is accessions or relapses occur, the eruption fades, dries up, and the nodules become absorbed without leaving a scar. The ulcerating mulaire lesions heal by cicatrization. In some cases only the miliary eruption appears and convalescence supervenes after several weeks.

As to the *etiology* of these conditions, verruga peruviana and Oroya fever, opinions have differed widely, although the majority of investigators have attributed a bacterial origin to the disease. Thus Barton at first described a bacillus which he thought was the cause of the malady, and later observed bodies in the blood which he believed were protozoa. By several investigators, however, these were regarded as products of cell degeneration. Paracolon bacilli were regarded as the cause of one stage of the disease by several investigators, while several others found acid-fast bacilli in lesions of the skin. Finally, very recently a species of Leishmania and one of Chlamydozoa have been held responsible for the lesions.

After studying these conditions for some time in Peru, our investigations led us to the conclusion that verruga peruviana and Oroya fever represent two distinct diseases. The former we believe is due to a virus which can be transmitted to several of the lower animals, and which produces definite lesions in them. Thus, for example, when the virus is inoculated intratesticularly into rabbits, after an incubation period of about fifteen to twenty-three days, a definite lesion usually appears. In dogs also by the same method of inoculation a somewhat similar lesion is sometimes produced. However, when repeated inoculations are made from testicle to testicle the virus becomes attenuated, and inoculations of this nature soon fail. The monkey is the most satisfactory animal for inoculation, and when the skin over the eyes is lightly scarified and a portion of a verruga nodule is rubbed into the abrasions, after an incubation period of from about fifteen to forty days, small papules appear which gradually enlarge and finally assume considerably the appearance of the lesions seen in man. They also have a similar histological structure. When monkeys are inoculated with the virus an interesting fact is that no generalized eruption of the skin occurs, but just as when this animal is inoculated with smallpox virus, only a modified form of the disease develops. The virus also shows other similarities to smallpox virus. Dr. Tyzzer and I have been able to show that monkeys may be successfully immunized against the verruga virus and in every instance when they have been reinoculated no lesion has developed. We therefore hope to have secured a satisfactory method of vaccination of man against this disease. We have stated that the disease verruga peruviana is due to this inoculable virus. The term virus is employed because we have been unable to detect by microscopical examination either in numerous fresh preparations often examined with the dark-field illumination, or in stained preparations made from the lesions, or in cultures made from them, or in sections of the tissues, any definite, visible microörganisms.

The histological study of sections of the lesions also shows that this disease is entirely distinct from Oroya fever. The very early verruga nodule possesses a very characteristic appearance. It consists of newly formed bloodvessels lying in edematous connective

tissue. These areas are frequently poor in cells, though a variable number of lymphocytes, larger plasma-cells, and polymorphonuclear leukocytes may be present. A striking feature is the number of endothelial cells about the early vessels and the amount of protoplasm which they contain. The outer layers of these cells continue to proliferate as the lesion advances, and gradually large islands of closely placed angioblasts are formed. Later on true fibroblasts appear and deposit their collagen fibers so that in the later lesions the structure comes to resemble more closely that of the fibrosarcomata.

In no other condition does one find such a striking and so characteristic a proliferation of the endothelial cells lining the bloodvessels as is encountered in the early verruga nodule, and it is this feature which particularly distinguishes the lesions from other pathological processes. The verruga nodule, therefore, constitutes a special form of granuloma, characterized in the early stages by the formation of new bloodvessels in edematous, connective tissue, and by marked proliferation of the angioblastic cells, forming masses or islands of closely placed cells, by the invasion of the connective tissue, with lymphocytes, plasma cells, and leukocytes, and as the lesion progresses by the formation of fibroblasts and the deposit of collagen fibrils.

In Oroya fever, on the other hand, there are no lesions upon the skin in uncomplicated cases. This disease we found to be due to a parasite of the red-blood corpuscles sufficiently distinct from the other hematozoa previously described to be placed in a new genus. The organism which we believe to be the cause of Oroya fever produces fever in man and in severe infections a rapid and pernicious form of anemia which results frequently in extreme prostration and death. In one of the cases studied by us the red-blood corpuscles numbered less than one million per cubic millimeter. At the autopsy of this case in addition to the evidences of severe anemia, the spleen was enlarged and showed numerous infarctions. No other organism to which death could be ascribed was found present. So far this organism has not been transmitted to the lower animals. The organism is both rounded and rod-shaped, and was observed in both fresh and in stained blood specimens. In fresh blood speci-

mens the rod-shaped parasites were observed to move in the direction of their long diameter, and to exhibit slight bendings and thickenings in their transition through the cells, and at times were seen to occupy all portions of them. The rounded bodies also were observed to change their position within the red-blood corpuscle. In stained preparations the rods measure from 1 to 2μ in length and from 0.2 to 0.5μ in thickness. They occurred singly, in pairs end to end, and in chains of several segmenting organisms. The ends of the rods are often more intensely stained. Single rods may show a deeply red staining granule at one end, while the remainder of the rod takes a bluish tint. This naturally suggests that the granules are of a chromatinic nature. Sometimes when the organisms appear in chains these deeply staining granules give a beaded appearance to the chain. It is evident that the organisms do not all lie in the same plane in the red-blood corpuscle, and are not superimposed upon it, as may be seen from some of the photomicrographs. In severe infections from 1 to 10 parasites may be seen in the same red-blood corpuscle, and the parasites have also been observed in the nucleated red cells in the peripheral circulation. From the anemia present in this condition, and from the number of infected corpuscles, it seems evident that the parasite eventually destroys the red-blood cells. To this parasite we have given the name of *Bartonella bacilliformis*. Its classification has been considered in another report.

The histological appearances observed in sections of the organs of those dying from Oroya fever are particularly interesting. Marked changes are encountered in the liver, spleen, bone marrow, and lymph glands. The *liver* shows areas of toxic degeneration which have apparently resulted from the activities of the parasite of the red corpuscles, *Bartonella bacilliformis*, and this fact would suggest that during the course of the disease in addition to the destruction of the red cells by the parasites developing in them, another pathological process results from the presence of a toxin in the circulating blood. The action of such a toxin seems to be revealed in the liver by the presence of extensive areas of necrosis of the central type, beginning about the hepatic veins. In these areas many of the liver cells in sections hardened in Zenker's solution show numerous

vacuoles in their cytoplasm which suggest spaces formerly occupied by fat, and in tissues hardened in formalin the characteristic stain for fat is obtained in these areas. Distinct zones of these cells containing fat droplets surround central areas of more marked necrosis in which many of the liver cells are very granular. Other liver cells about the areas appear homogeneous and hyaline and stain intensely with eosin. Much granular material is present in the sinusoids and numerous endothelial phagocytes frequently containing erythrocytes, erythroblasts, and polymorphonuclear leukocytes are present in the periphery of the necrotic areas between the liver cells. While there is not extensive pigmentation of the liver, moderate amounts of pigment in granules or small masses may be seen within the endothelial phagocytes and in a few endothelial cells lining the sinusoids. Occasionally small granules of pigment may be seen in the liver cells. Most of this pigment does not give the iron reaction; it is yellowish or brownish in color, and not black. Crystals of hematoidin are also present.

The *spleen* is enlarged and shows numerous infarctions. In sections the edges of the infarcted areas are much congested and show leukocytes migrating into the necrotic tissue. Many of the veins show thrombosis suggesting endothelial injury from some toxic or infectious agent. At the periphery of many of the splenic nodules just outside the capsule areas of necrosis are visible in which there is marked deposition of fibrin. There is a large amount of pigment in the spleen, which occurs in small or larger masses and also in fine granules. It is yellowish or yellowish-brown in color, and is present in both the endothelial leukocytes and also free in masses between the splenic cells. The pigment is not black, and does not resemble black malarial pigment. It resembles melanin in that it does not give the iron reaction. Whether in Oroya fever the anemia partially results from the destruction of the red-blood cells through the circulation of hematin, as W. H. Brown believes to be the case in malaria, at the present time is not clear. *Bartonella bacilliformis* evidently produces no pigmentation in the red cells in the peripheral circulation. No malarial parasites are visible in the splenic sections. The spleen is rich in pulp and much congested and many nucelated red-blood corpuscles are visible. Endothelial phagocytes

frequently containing red-blood cells are also present in abundance. In the bone marrow there is also striking evidence of phagocytosis by endothelial leukocytes of the red corpuscles in various stages of development, and of polymorphonuclear leukocytes. It seems probable that this extensive phagocytosis which is evident in the liver, spleen, and bone marrow is also an indication of the action of a toxic substance which has led to chemical changes or injury to the engulfed cells. In the lymph glands the most striking, histological feature which at once attracts the attention is the presence of large, swollen, endothelial cells, sometimes free in the lumen of the vessel, at other times still attached to the walls. In some instances a single endothelial cell is so swollen that it will almost occlude the entire lumen of the vessel. These cells are in various stages of degeneration. Many of them contain rounded and rod-shaped bodies, and it seems evident that one stage of the life cycle of the parasite is passed within these cells. Dr. Tyzzer and I have already reported before the Society of Pathologists of Bacteriologists upon this subject.

Returning to the disease verruga peruviana, it is quite evident that it represents an entirely distinct disease, and that it is not a form of frambesia. In our opinion, anyone who has had a wide experience with either disease would not confuse, from a clinical standpoint, the one with the other. Only in the distribution of the lesions, sometimes, and in the fact that in both small nodular tumors appear upon the skin, is there any resemblance in the two diseases. A brief description of the skin lesions of verruga peruviana has already been given. The most characteristic feature of the yaws lesion is that the primary one is a papule which after about a week becomes moist, developing a yellowish secretion which dries into a crust. The verruga lesion has an entirely different appearance. It is practically never crusted. The most characteristic feature in its appearance as we have seen is that the skin is smooth, tense, and translucent over it, and that the superior surface of the lesion resembles very much a cherry, at the height of the disease. Frambesia is also contagious, while verruga is not. In frambesia there is frequently a distinguishable point where the initial lesion develops, in verruga this is not so apparent. However, there are other more

decisive points of difference. Thus from an etiological and pathological standpoint, the two are entirely distinct infections. In a very careful study of the lesions of verruga peruviana as I have emphasized we have been unable to detect *Spirocheta pertenuis* or any other visible microörganism. In the very numerous experiments in which fresh material from the human verruga lesions has been injected into the rabbit's testicle, the lesions produced have not resembled those which result from the inoculation of material from the lesions of frambesia cases, and again no spirochetæ have been found in them. In the intratesticular lesion which results from the inoculation of frambesia material, as was first shown by Nichols, spirochetæ are abundant. Finally, the disease verruga peruviana is not cured by injections of salvarsan, as I first showed in August, 1910, to be invariably the case with frambesia. The lesions of the skin of verruga peruviana seem to be entirely uninfluenced by injections of this substance, while in frambesia they disappear very rapidly following its injection.

It is not deemed necessary to consider here in detail the differentiation between the histological structure of the lesions of verruga and those of frambesia. In frambesia the lesions affect the epithelium rather than the cutis. The surface epithelium is greatly increased and numerous down-growths occur. The epithelial cells are usually degenerating and swollen and hyperkeratosis may be present. Often there are sharply circumscribed areas containing polymorphonuclear leukocytes and detritus. Cellular infiltration of polymorphonuclear leukocytes, of large and small mononuclear leukocytes, eosinophiles, plasma cells, mast cells, connective-tissue cells, and red-blood corpuscles are present. In the older lesions the plasma cells usually predominate. There is not the endothelial proliferation and perivascular proliferation so frequently seen in syphilis. The lesions affect the epithelial layer rather than the cutis. The tissues often show considerable edema. In verruga the most striking feature as you have seen in the illustrations is the extensive endothelial proliferation occurring about newly formed bloodvessels, a condition which is not observed in frambesia. The histological appearances of the verruga lesions have already been considered in detail and from this description it is evident that

from a pathological standpoint, as well as from a clinical one, the two diseases frambesia and verruga peruviana are also distinguishable.

While discussing the differentiation of verruga peruviana from frambesia, it may be advisable briefly to refer to its differentiation from syphilis. From what has already been said regarding the absence of spirochetæ in not only the human lesions of verruga, but particularly in those produced in the rabbit's testicle with verruga material, and from the complete resistance of the disease to treatment with salvarsan, it would appear evident that the disease is not a form of syphilis. The Wassermann reaction was negative with one exception in the cases of verruga which we studied. In performing these experiments cases of syphilis were used as positive controls, and normal cases for negative controls. In 9 cases of verruga in which a well-marked eruption was present, the reaction of the serum was also investigated in relation to the fixation of complement with a specific antigen prepared from a verruga nodule. In none of these cases was a fixation of complement obtained. It is noteworthy in this connection that according to Castellani and Bowman fixation of complement occurs with the serum of yaws cases when yaws antigen is employed. Baermann found that in yaws as in syphilis the Wassermann reaction is present.

In the disease ulcerating granuloma of the pudenda the histological appearance of the lesions varies considerably. In general it may be stated that the connective tissue of the corium swells and disappears, and its place is taken by a round-cell infiltration which consists of leukocytes, plasma cells, mast-cells, and connective-tissue cells. Giant cells are usually not found. The cells of the epidermis are swollen, often hyaline, and show mitosis. In the periphery of the lesions there is round-cell infiltration in the upper region of the corium. The papillæ become increased in length. In the older lesions there is no caseation, but the tissues become edematous and much cicatricial connective tissue is found.

In regard to the etiology of the affection ulcerating granuloma, Donovan, Siebert and Flue have described small, rod-like or coccus-like parasites, 2 x 1μ, which are said to lie singly or in groups in mononuclear cells obtained in microscopical preparations made from

ulcerations. Several observers, De Beaurepaire, Aragao, and Vianna have cultivated these capsulated, coccus-like bodies which were believed by Donovan and Siebert to be protozoa. On the other hand, Wise and Cleland have described a spirocheta as the cause of the disease, naming this organism *S. aboriginalis,* and Martini has cultivated a diplococcus on blood agar and bouillon from a case. Very recently Wise has found spore-like bodies which he states seem to represent some phase in the life-history of a protozoan organism. It seems probable, however, that some of these microörganisms, and particularly the spirochetæ may be merely secondary invaders, and from my own observations the etiology of this affection does not as yet seem to me to be definitely determined. From our knowledge of the causative agent in verruga peruviana, it would appear advisable to perform more extensive experiments in the inoculation of animals, particularly of monkeys, with the idea of attempting to transmit to them the etiological factor.

DISCUSSION

Dr. Simon Flexner: You said nothing about the virus of verruga.

Dr. Strong: As to whether it is filterable or not?

Dr. Flexner: Yes.

Dr. Strong: The time was so short that I only spoke of the virus to the effect that it can be transmitted definitely to some of the lower animals, rabbits and monkeys, producing definite lesions in them.

Dr. Flexner: You mean you transmit the disease to animals?

Dr. Strong: Not the disease but only a modified form is produced by the transmission of the virus since only a localized lesion develops in the animal.

Dr. Flexner: Do you know what the virus is?

Dr. Strong: We do not know the exact nature of the virus and so far we have not been able to filter it successfully. Cultivation experiments have been made.

Dr. Flexner: So far it is invisible and does not belong to any of the others spoken of.

Dr. Strong: No, it is apparently quite distinct. Later on, I think the virus probably will be shown to be filterable. It may be that we will have probably much the same history to go through in regard to this virus that we did in regard to the one of smallpox, which was formerly considered non-filterable. We have made attempts to filter this virus, and we have found so far that monkeys cannot be successfully inoculated with the filtrate and lesions will not develop in them, and such monkeys are not rendered immune as may be seen if reinoculated with the unfiltered virus. Of course, the organism may go through the pores of the filter and still be in too dilute a state to produce a lesion in a monkey. A monkey is not a very susceptible animal to the virus, since as I have said only a localized lesion and no generalized eruption results when it is inoculated.

Dr. Flexner: Is it a chronic disease?

Dr. Strong: Yes, there is an acute stage but there is also a subacute or rather chronic one, as the attacks usually last from two to three weeks, but relapses frequently occur one after the other.

Dr. Flexner: Has salvarsan any effect on the disease?

Dr. Strong: No.

Dr. Flexner: There are no spirochetæ?

Dr. Strong: No, and no other visible organism is present.

THE RELATION OF THE PURGATIVE ACTION OF MAGNESIUM SULPHATE TO PERISTALSIS, AND THE GENERAL LAW OF CROSSED INNERVATION

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Permit me to say at the start, that, while the subject I intend to discuss here in particular is the inhibitory rôle of magnesium salts in its relation to the production of intestinal peristalsis, my chief object is to bring before you certain general views I hold now, and have held for many years, on the subject of inhibition in general and the rôle which it plays in the mechanism of all sorts of movements in the animal organism.

I shall begin the discussion of the relation of magnesium salts to peristalsis by calling your attention to two sets of facts which seem to contradict one another. It is a well-known and well-established fact that magnesium sulphate, or Epsom salts, is one of the most efficient purgatives. There have been many discussions as to the course of action of saline purgatives. According to one view, which has undergone many variations in its details, the cause of the purgation consists in the capacity of the saline to bring about an accumulation of liquid within the lumen of the intestines. We need not discuss here the nature and origin of this liquid. For our purpose it suffices to say that, no matter from what cause liquid accumulates within the intestines, its mere presence would not cause purgation without the mediation of peristaltic movements of the intestinal canal. It is a known fact

that the presence of large quantities of liquid within a paralyzed intestine does not lead to evacuation. According to another view which in recent years has been brought forward again by pupils of Jacques Loeb the cause of action of certain purgative salts consists directly in their ability to stimulate the nuero-muscular apparatus of the peristaltic mechanism. According to all views, then, peristaltic movements are indispensable for purgation and therefore magnesium sulphate as an efficient purgative is expected to increase, or at least not to inhibit, the peristaltic movements of the intestines. I hardly need to add that under the term peristalsis is generally meant a progressive movement of a vermiform character which, in our special case, means a vermiform movement of the gastro-intestinal canal running in aboral direction.

Now in apparent opposition to the mentioned fact I have to enumerate a number of observations which were safely established in our laboratory in the course of the last few years. In experiments carried out by Auer and myself several years ago in which the behavior of the intestines of rabbits was observed in a warm bath of normal saline, we found that intravenous injections of magnesium salts stop peristaltic movements promptly. Usually not much peristaltic movement of the intestines can be seen when the abdomen of a rabbit is opened. In order to observe the effect of magnesium sulphate, peristaltic movements had to be brought on by artificial means: by intravenous injections of sodium sulphate, barium chlorid, physostigmin or ergot, or by the destruction of the spinal cord. The peristaltic movements brought on by these means were sometimes of a violent character. All these peristaltic movements were either completely inhibited, or at least greatly reduced, by an intravenous injection of a solution of magnesium sulphate (or magnesium chlorid).

In a later series of experiments, carried out by Don R. Joseph and myself, a method was employed in which the peristaltic movements could be studied in animals whose abdomen was closed. The abdomen of rabbits was opened under proper anesthesia, and catheters, bearing at one end a small balloon, were inserted into the lower part of the duodenum and into the stomach; stomach, duodenum, and abdomen were then properly closed. In the fol-

lowing days the protruding end of the catheters was connected with a graphic apparatus and tracings presenting the peristaltic movements of the stomach and the duodenum were obtained. There were good spontaneous movements of the stomach and the duodenum in nearly all cases. We have, then, established beyond a doubt, that the action of magnesium sulphate upon the stomach and the duodenum was under all circumstances only of an inhibitory character. Whether the peristaltic movements were spontaneous in origin, or were brought about or intensified by barium chlorid or other substances, an intravenous injection of magnesium sulphate, even in an isotonic concentration, invariably caused an immediate inhibition, or at least an unmistakable reduction of the peristalsis, lasting for some time even after the injection had ceased.

These experimental results were obtained, as stated before, by intravenous injections of the magnesium salts. However, I am now in a position to state that the same inhibitory results can be readily obtained when the magnesium solutions are introduced into the lumen of the gut. Auer and I found that magnesium salts, when introduced into the lumen of the gut, are readily absorbed and may cause respiratory paralysis and death of the animals within a short time after the injection. Recently I have studied the effect of such a direct introduction of magnesium salts into the lumen of the gut upon the behavior of the peristaltic movements of the latter. I found that the gut becomes practically paralyzed. I shall mention here one striking result. When the trachea of an animal is clamped and the animal thus killed by asphyxia, the exposed intestines show more or less strong peristaltic movements. When, however, a solution of magnesium salts was previously introduced into the lumen of the gut, no part of the gastro-intestinal canal shows movements worth mentioning during or after the asphyxia.

These various experimental observations show unmistakably that magnesium salts, whether given intravenously or introduced into the lumen of the gut, not only do not cause any peristalsis of the gut, but positively inhibit it, when it is present. The puzzling question which now presents itself is this: If magnesium sulphate

causes a suppression, an inhibition of the peristaltic movements, and only an inhibition, how can it bring on purgation in which, as we have seen above, peristaltic movements of the gut are an indispensable factor?

To answer this question I shall have to enter into an analysis of inhibition and the rôle it plays in peristalsis. You all know what is meant by inhibition. The best known type of it is the phenomenon with which you are all acquainted, the fact that stimulation of the end of the vagus which goes to the heart stops the beating of that organ. The heart is a muscle. A nerve going to a muscle we usually term a motor nerve. Stimulation of such a nerve causes contraction of the muscle pertaining to it. But stimulation of the end of the vagus which goes to the heart stops the heart from beating. That is inhibition. Numerous other examples and other forms of inhibition are now well known. One of them is, that stimulation of the end of the splanchnic nerve which goes to the intestines, stops peristalsis of the gut; it inhibits the peristalsis. Here we have some evidence that the phenomenon of inhibition may be connected with the peristalsis of the intestines. However, the most striking fact that inhibition is actually concerned in the peristaltic movements of the digestive tract, was made by us thirty-four years ago in our studies of the function of deglutition. We have then first established that after each beginning of a deglutition various parts of the esophagus develop a peristalsis at various intervals according to their distances from the tongue and pharynx. For instance, the peristalsis of the cervical part of the esophagus sets in about two seconds after the beginning of deglutition; the esophagus in the upper part of the thorax begins to contract in about three seconds, and the part of the esophagus above the diaphragm begins to contract about six seconds after the deglutition. These data were obtained from observations upon my own esophagus. Now we discovered in the course of these studies, that when the deglutitions are repeated, say in less than every three seconds, the upper part of the thoracic esophagus does not contract after each deglutition but only after the last deglutition has taken place. The same applies for the cervical as well as the lower part of the esophagus. In other words, with each deglutition which sends

down an impulse for a contraction of the peristalsis, also an inhibitory impulse is sent down along the esophagus for the purpose of inhibiting any possible contraction which may be present in any part of the esophagus, due to a previous act of deglutition. I may say here that each deglutition inhibits also the presence of a tonus in the esophagus. This physiological phenomenon reminds one of the precautions which are taken when an express train is sent off; along the entire road telegraphic messages are sent, to keep the tracks free. That is the sense of the inhibitory wave which runs ahead of the peristaltic contraction and keeps the track free.

Some thirty years ago I tried to generalize this point of view, to apply it to all functions of the body which require definite movements. I stated then, that, for instance, for the performance of the extension of the leg, it is necessary that the flexors should be inhibited from being contracted simultaneously, or from remaining in a state of tonus. At that time I illustrated the actual occurrence of such antagonistic relations by the behavior of the function of respiration; during each inspiration the contraction of the expiratory muscles are inhibited and during each expiration the diaphragm and other inspiratory muscles are suppressed, inhibited.

I wish to dwell here a little longer on that subject. You probably know that these relations of flexors and extensors, as I anticipated them many years ago, have been brilliantly studied since 1895 by Sherrington, who terms the relations of flexors and extensors "reciprocal innervation." That designation is for these specific relations proper enough, because just as the flexors become inhibited when the extensors have to contract, the extensors also become inhibited, when the flexors are contracted—it is then a truly *reciprocal* innervation process. But when we apply these relations to a canal in which movements go on only in one direction, there is, of course, only one-half of this process. It is always only the lower part of the canal which has to be relaxed when the upper part is contracting. A true antiperistalsis does not exist. In order to comprise all these phenomena under one head I termed the relations under discussion as "contrary innervation." It produces simultaneously a contraction in one part and an inhibition in another, in the contrary part. That means, two parts which are

concerned in a single function, are simultaneously innervated in a contrary way. The upper part of the canal is contracted in order to move the contents downward and the lower part is relaxed in order to remove any obstacle to this motion.

We shall now turn back to the digestive tract. I shall mention here first, that on the basis of these considerations we discovered long ago that with each act of deglutition the tonus of the cardia becomes inhibited—to open the gate into the stomach for the entrance of the contents which is swallowed down. In recent years Joseph and I found that during each contraction of the pyloric part of the stomach an inhibition of the movements of the duodenum takes place. Cannon and Lieb found that during a peristaltic contraction of the esophagus a simultaneous relaxation of the stomach makes its appearance. Finally, Lyman has observed that the colon becomes motionless and relaxed while the material is driven through the ileocolic sphincter by peristalsis in the ileum. All these observations have evidently that one background in common, namely, that for the purpose of moving downward the contents of the gastro-intestinal canal, the distal part of the various sections of the canal becomes inhibited, while the adjoining proximal (upper) part of the corresponding section gets into a state of contraction—a manifestation of the Law of Contrary Innervation.

Of greater interest to our problem is the instructive observation which was made by Bayliss and Starling some seventeen years ago, namely, that a stimulation of the intestines at any place causes a contraction above the point of stimulation and a relaxation or inhibition of the part of the gut below the point of stimulation. Bayliss and Starling called this phenomenon the Law of the Intestines. But it is evident that this phenomenon is the law not only of the intestines, but of the entire digestive canal and that it is, furthermore, a part of the phenomenon which I termed "Contrary Innervation."

The outcome of the foregoing facts under consideration, bearing upon intestinal peristalsis, is evidently this: A peristaltic movement does not consist merely in a vermiform downward moving contraction; peristalsis is made up of two simultaneous phenomena: a contraction of the upper part and a relaxation or an inhibition of

the lower part of the section of the gastro-intestinal canal, engaged in the act of moving downward some of its contents.

Bayliss and Starling have shown that this dual response of the intestine to a single stimulus takes place even when the intestines are freed from their extrinsic innervation. They thought that the process is of a myogenic origin; but Magnus has shown conclusively that it is connected with Auerbach's plexus, the myenteric plexus, located between the longitudinal and circular sheaths of the fibres of the intestinal muscularis. We may, therefore, formulate our conclusion in the following terms. A stimulation of the myenteric plexus produces simultaneously a double effect, a contraction of the muscle fibres above, and the inhibition of any contractions below the point of stimulation.

I shall now turn my attention to the relation of magnesium sulphate to the phenomenon of inhibition. About sixteen years ago, when studying the effect of intracerebral injection of various salts, I came across the following surprising fact: While the injection into the cerebrum of many other salts produced characteristic convulsions, the injection of a few drops of a 5 per cent. solution of magnesium sulphate caused the rabbit to turn over on one side and remain lying in a state of stupor and relaxation. With a long-standing interest in the phenomenon of inhibition it was quite natural for me to interpret the stuporous and relaxed condition of the animal as possibly being a state of inhibition. In the many studies of the action of salts upon the animal organism to be found in the physiological and pharmacological literature, the effects observed and studied were always those of the exciting action of the salts. It was from the point of view that possibly the magnesium ion in the body is chiefly concerned in the inhibitory processes, that we started our various studies on the effects of magnesium. It became a working hypothesis; we did not yet come across definite weighty facts which are capable of disproving this hypothesis. As to the relations of magnesium salts to the gastro-intestinal canal, it has been stated already before, that in the studies of Auer, Joseph, and myself no other effect was found but that of inhibition of the peristaltic movements of the gut.

We come now to our original question; it is this. On the one

hand, it is a sure fact that magnesium salts cause purgation, a process in which peristalsis must be a factor; on the other hand, the extensive experimental studies revealed the unmistakable fact that magnesium salts inhibit intestinal peristalsis. How can we reconcile these apparently contradictory facts? My answer to this question, given merely in a general way, is this: (1) The phenomenon of peristalsis consists not only in a contraction of a certain part, but in a contraction of the proximal and a *relaxation of the distal part* of a section of the gut. (2) The effect of magnesium sulphate on peristalsis may consist chiefly in its relation to the inhibitory part of the phenomenon of peristalsis.

As I have just indicated, my answer to the central question shall be only of a general character; I am unwilling for the present to enter upon definite statements as to the particulars, how magnesium affects the peristalsis. I am quite confident that details which I may venture to state now, will have to be modified by facts which future experimental investigations are sure to bring to light. I shall, however, try to continue our analysis by discussing briefly a few points which may have some bearing upon our subject.

1. We have seen above that a stimulation of any part of the gut causes, by means of the intrinsic myenteric plexus (and probably also by the aid of the extrinsic innervation), a contraction above and a relaxation below. How strong the contraction of the part above may be, and how intensely is the inhibition of the part below, and how far it may extend, depends upon a variety of circumstances. In the first place, we must here, as everywhere, distinguish between irritability and stimulation. Increase of irritability alone can bring out no action without the incident of a stimulus. The irritability of the concerned innervations may be low or high and may concern the exciting and inhibitory phases in various degrees. For instance, magnesium salts may increase exclusively or essentially the irritability of the inhibitory phase, while other salts, for instance, sodium sulphate, may increase preferably or exclusively, the irritability of the exciting phase. There is good reason for the assumption that the increase of irritability occurs through the circulation; but we have no definite evidence that this may not occur also by mere action upon the periphery.

Again, stimulation may affect preferably the exciting phase or the inhibitory. But we are rather inclined generally to assume that a stimulus affects, as a rule, both the exciting and the inhibitory phases simultaneously. We are also inclined to assume that the point of attack of a stimulus is to be found mostly at the periphery. We hardly need to add that a stimulus may be weak or may be strong.

Taking all these points together, it can be seen at a glance, how variable the effects of some substances upon the gut may be. With a low irritability of certain sections of the gut and with a comparatively low stimulus from the periphery, the effect may be all together circumscript, and the result may be not peristalsis, but only "segmentation," the effect of each stimulus not being an intense contraction above and not an extensive relaxation below. With an increased irritability and with a moderately strong stimulus, there may be a fair contraction above and a fairly extensive relaxation below, and the result will be a peristalsis, extending over a fairly large section. With a strongly increased irritability of both phases and with a strong stimulus, the result may be a rapid peristalsis, running through the entire gut within a very short time, a condition which we termed "peristaltic rush."

2. A brief discussion of peristaltic rush will not be amiss here. As it was stated, by "Peristaltic Rush" we designated the phenomenon of a very rapid peristaltic movement running downward through the entire small gut within a fraction of a minute. This phenomenon was observed for the first time by Van Bram-Houckgeest some forty years ago in rabbits dying from asphyxia. He termed it "Rollbewegungen." Several years ago Auer and I succeeded in producing this phenomenon practically at will in living rabbits. The method we used consisted in injecting intravenously antagonistic substances, that is, one substance which favors contractions of the gut, and another which favors the inhibition of such contractions; for instance, ergot and magnesium sulphate.

3. We have to call attention to the fact that our experimental studies of the inhibitory effect of magnesium salts upon the peristalsis of the gut were made either by administering magnesium sulphate intravenously or by injecting it into the lumen of the small intestines. However, when administering magnesium sul-

phate through the mouth (as it is done for the purpose of purgation) while the salt passes through the stomach, it meets there with sodium chlorid and with some carbonates. It is, therefore, possible and even probable that parts of the magnesium sulphate become converted into sodium sulphate and magnesium carbonate. Sodium sulphate is soluble and is readily absorbed. From the experiments of MacCallum and of Auer we know that sodium sulphate, when given intravenously, is apt to bring on some peristalsis. Magnesium carbonate is not soluble and remains within the gut probably entirely unabsorbed. We know that magnesium carbonate is capable of acting as a purgative. The insoluble carbonate acts possibly within the gut in two ways: On the one hand, it attracts liquid into the lumen of the gut, thus distending it, and, on the other hand, the carbonate is likely to serve as a chemical stimulus directly upon the mucosa. At any rate, it is not impossible that that part of the magnesium sulphate which has been converted into a carbonate acts within the gut as a stimulus, calling forth peristaltic movements. On the other hand, the part of the magnesium sulphate which is converted into sodium sulphate may be the means of increasing the irritability of the exciting phase of the peristalsis; it may serve also as a stimulus upon the neuro-muscular apparatus. The remaining unconverted portion of the magnesium sulphate increases the irritability of the inhibitory phase of peristalsis. Now we have seen above that by the administration of antagonistic substances, that is, substances, one of which increases the exciting phase, while the other increases the inhibitory phase of peristalsis, are capable of calling forth a "Peristaltic Rush," that is, a peristaltic wave which runs very rapidly through the entire small intestine within a very short time. We can therefore easily conceive, that the purgative action of magnesium sulphate, when administered by the mouth, results from the fact that a part of it acts by increasing the inhibitory phase of peristalsis, while other parts, by being converted partly in sodium sulphate and partly in magnesium carbonate, increase the irritability of the exciting phase of peristalsis, and serve as an inciting stimulus to start peristaltic movements. The result is the development, after some time, of partial and perhaps complete peristaltic rushes.

I wish to repeat again that I offer this detailed analysis of the action of magnesium sulphate merely as a preliminary hypothesis. Future experimental work will throw more light upon these questions.

4. I shall permit myself to state here in a few words my general conception of the various effects which may result from the simultaneous actions of exciting and inhibitory factors upon the functions of the animal body. The resultant effects of the antagonistic actions can be of a threefold nature which may be designated as *tonus*, *rhythm*, and *peristalsis*. (1) The resultant effect of the antagonistic actions may be *manifest at the same place and at the same time*. This is a *tonus*. The degree and the character of the tonus depend upon the preponderance of one or the other factor. (2) Or the effect of both antagonistic factors may be *manifest at the same place, but at different, alternating times*. It is then a *rhythm;* contraction alternates with inhibition. (3) Or both effects of the antagonistic factors may be present *at the same time but manifest themselves simultaneously at different* parts. The resultant is then a *peristalsis:* a contraction above and an inhibition below.

A POSSIBLE FACTOR IN THE PRODUCTION AND DISTRIBUTION OF EDEMA

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Is there one among us who has not been struck, if not puzzled, by the curious distribution of edema, especially in cases obviously of mechanical obstruction to the circulation? We see, for instance, two cases of mitral disease with failure of the myocardial compensation. The physical signs and symptoms taken altogether indicate lesions similar in kind, as well as degree, and also an approximately equal myocardial weakness. The parallelism between the two cases may be accentuated by an equal rapidity and degree of improvement under, for all practical purposes, identical treatment. The sequence of events is mechanically impeded circulation, dilatation of the right heart annulling compensatory hypertrophy, over-plus of blood in the venous system, stasis, and dropsy. A difference in the degree of the dropsy in the two cases may be readily accounted for by differences in the lesion, valvular, myocardial, or both, which elude any means now in our power to estimate. But it would seem that the distribution of the edema should be essentially the same. It is, however, notoriously not so. In one case we see dropsy chiefly or only in dependent parts, especially the legs; in another the great serous sacs are markedly involved with a varying degree of stasis in the lungs, liver and kidneys and little or no anasarca; in still another stasis shows itself mainly in an enlarged liver; in short, seemingly similar mechanical conditions show results which vary far more widely than one would, off-hand, expect.

Long ago, a possible, at least partial, explanation occurred to me. I have not seen it in print or heard it suggested, and venture to lay it before you, keenly realizing its hypothetical nature, and how far removed it seems, at present, from direct evidence. The Bertillon

system shows that by a sufficient number of accurate measurements any person can be distinguished from every other person. Even more remarkable proof of the individuality of the individual is afforded by the fact that no two persons have the same finger prints. Is it not at least possible that analogous variations may exist in the texture of the tissues, of the organs, in the blood, or one or another of its constituents, which may be a factor in the distribution of edema.

In the urticarias, perhaps especially the giant form, and in angioneurotic edemas, a nervous element must play an important part; but it would seem possible that individual peculiarity of tissue may be a factor in the localization of the striking superficial changes.

THE TOTAL NON-PROTEIN NITROGEN AND THE UREA OF THE BLOOD IN HEALTH AND IN DISEASE, AS ESTIMATED BY FOLIN'S METHODS[1]

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Summary and Conclusions. Analysis of the blood for total non-protein nitrogen and urea nitrogen have been made by the methods of Folin in five healthy adults and 142 hospital cases.

1. In the fasting healthy adult the total non-protein nitrogen varied between 22.9 and 25 mg. per 100 c.c. of blood, and the urea nitrogen between 12 and 14 mg.

2. The effect of a full meal with meat in the case of the healthy adult was a rise of total non-protein nitrogen averaging 4.7 mg., and of urea, averaging 2.5 mg.

3. In both chronic interstitial and chronic diffuse nephritis the cases without symptoms of uremia showed normal or moderately elevated values; the uremic cases, with one possible exception, showed a great increase in both nitrogen and urea.

4. The excretion of phenolsulphonephthalein was roughly proportionate to the degree of retention; the cases with 100 mg. or over of total nitrogen all showed 5 per cent. or less phthalein excretion. Many cases, however, with a considerable impairment of phthalein excretion showed no signs of retention, and a moderate amount of retention of waste nitrogen often occurred with no impairment of the elimination of phthalein.

[1] This article is printed in full in the Archives of Internal Medicine, 1914, vol. xiv, pp. 620–649.

5. The proportion of urea nitrogen to the total non-protein nitrogen in disease varied from 32 per cent. to 85 per cent. Where the nitrogen was normal the urea usually was about one-half the total nitrogen, where it was elevated the urea usually but by no means always constituted about 70 per cent. of the whole. No reasons could be found for these variations. The determination of the total non-protein nitrogen alone is therefore more valuable than that of the urea alone.

6. The determination of the total non-protein nitrogen is of the greatest value in the diagnosis of uremia. Amounts of 100 mg. or over were met with in only two conditions besides uremia, viz., acute intestinal obstruction, and profound anemia from hemolysis. Only one case of uremia without marked increase in nitrogen was seen out of a total of eight cases.

7. The determination of the total non-protein nitrogen is a great aid in the prognosis of chronic nephritis. All cases showing over 100 mg. died, the longest period of survival being eighty-eight days.

8. The results of blood analysis furnish the best guide as to the diet to be given in nephritis; cases with a considerable retention require a restriction of the protein, and by this means a return to normal figures may be brought about, if the azotemia is not too pronounced. In cases of outspoken uremia, however, no marked reduction of the azotemia has resulted from a protein-poor diet. Nephritis with a normal amount of non-protein nitrogen does not call for any *marked* decrease of protein in the diet.

9. In chronic passive congestion of the kidneys there is little or no retention of nitrogenous waste products.

10. In pyelitis the presence of azotemia probably indicates involvement of the parenchyma of the kidney.

11. A marked elevation of the non-protein nitrogen or urea renders the patient a poor operative risk, and the azotemia should be overcome by diet, if possible, before an operation is attempted in all cases where delay is permissible. In hypertrophy of the prostate, for example, a low protein diet may be combined with drainage of the bladder as a preliminary to operation.

12. Chronic lead poisoning was accompanied by evidence of retention in all the cases examined.

13. The eclampsia of pregnancy seldom shows a marked increase in non-protein nitrogen and urea. It is therefore distinct from uremia. Analysis of the blood will usually serve to distinguish between uremia and eclampsia.

14. In acute intestinal obstruction a tremendous increase in the nitrogenous waste products was found in all of the three cases examined. A return to normal took place in the two which recovered.

15. Compensated valvular disease of the heart, aortic aneurysm, acute pericarditis with effusion and acute endocarditis in the absence of disease of the kidneys, all showed normal values.

16. In acute lobar pneumonia a considerable increase was met with in the majority of cases, reaching its maximum toward the crisis, but bearing no relation to the time at which resolution took place. Typhoid fever, acute articular rheumatism and uncomplicated scarlatina showed normal figures.

17. Syphilis showed a considerable degree of retention in 36 per cent. of the cases examined, evident in all stages of the disease.

18. In cerebral hemorrhage, hysteria and neurasthenia no increase was found.

19. Severe anemia due to hemolysis showed a marked retention, reaching in one case 100 mg. of nitrogen.

20. In uncomplicated diabetes the values were normal; both cases examined in coma showed retention.

21. The administration of thyroid extract in the two cases of myxedema caused an increase in both nitrogen and urea. Both cases were complicated with chronic nephritis.

22. In exophthalmic goitre the blood nitrogen and urea were normal in amount.

23. No changes were met with in malignant disease which could not be ascribed to a complication with renal disease.

24. In a case of acute yellow atrophy the proportion of urea nitrogen to the total non-protein nitrogen was decreased although there was a considerable degree of azotemia.

DISCUSSION

Dr. William Hanna Thomson: I wish merely to make an observation upon the remarks of the essayist, and that is, that uremia is a very complex subject and by no means synonymous with deficient elimination of urea.

I was called in consultation to see a case in which not a drop of urine had entered the bladder for eight days, the reason for this being that one kidney, thirteen years before, had been obliterated by a calculus, and the patient went along for that length of time in apparently perfect health, not knowing he had only one kidney, when that also became impacted with a collection of calculi. When I saw the case the man had been in that condition for eight days, but showed no symptoms whatever except contracted pupils and a slight twitching. I told the doctor in attendance to cut down upon the ureter or the patient would soon die. He declined to do it because the patient did not show a single sign of uremia. I told him the patient would die though he manifested nothing but progressive asthenia. He declined to operate and the patient died, not having had a headache, convulsions, vomiting, or any of the ordinary signs of uremia. This patient died apparently from pure weakness. They held a postmortem examination, and the patient's physician said Professor Thomson made a mistake; the ureter was blocked by five stones instead of one.

THE INFLUENCE OF DIET UPON THE NECROSIS CAUSED BY HEPATIC AND RENAL POISONS

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WIDE variation in the susceptibility of different individuals to the same poison has suggested the possibility that an apparently unrelated factor, such as diet, may modify the effect of a toxic substance. Individual susceptibility is illustrated by the occurrence of delayed chloroform poisoning. It is well known that chloroform administered to animals causes necrosis of the central portion of each hepatic lobule and the severity of the lesion is roughly proportional to the quantity of chloroform which has been administered. Nevertheless, experiments in which chloroform has been administered during the course of other investigations have shown wide variation in the susceptibility of different individuals of the same species. Quantities which given by mouth usually have little effect occasionally produce death with multiple hemorrhage or jaundice and at autopsy the liver shows widespread necrosis. The experiments which will be described, furnish no comprehensive explanation of such individual susceptibility, but suggest that diet may have a profound influence upon the severity of intoxication and of disease.[1]

The most noteworthy investigation of the effect of diet upon resistance to intoxication is that of Reid Hunt, who studied the behavior of aceto-nitril in mice and guinea-pigs fed upon various substances. Certain diets, notably dextrose, oatmeal, liver and kidney, greatly increase the resistance of mice to aceto-nitril.

[1] Some of these experiments have been described in the Jour. of the Amer. Med. Assoc., 1914, lxii, 895; 1914, lxiii, 136.

Eggs, milk, cheese and various fats, greatly lower the resistance of mice to aceto-nitril. Hunt refers increased susceptibility to increased disintegration of the aceto-nitril molecule with formation of hydrocyanic acid.

The purpose of the present studies has been to determine if diet can influence the incidence or extent of a readily demonstrable lesion. Lesions of the liver have been produced by substances which have a peculiar affinity for the parenchymatous cells of the organ. Chloroform administered by inhalation, by mouth or by subcutaneous injection causes necrosis of the hepatic cells in the centre of each lobule of the liver and may implicate four-fifths of each hepatic lobule. Fatty degeneration may occur in the heart muscle, in the kidney or in other organs, and necrosis of cells of the convoluted tubules of the kidney is observed (rats) but the substance exhibits a selective action destroying the hepatic cells and leaving other tissues by comparison little altered. Phosphorus has been selected as another example of substances which exhibit an affinity for the liver; it produces fatty degeneration which is more advanced in the liver than in other organs.

In a second group of experiments substances which exhibit a selective destructive action upon the kidney have been used. Both potassium chromate and uranium nitrate cause necrosis of the cells of the renal tubules but produce no necrosis of the liver or of other organs. It is well known that these substances which have been widely used for the experimental production of nephritis cause albuminuria and the formation of urinary casts.

Method. White rats were used because they are omnivorous and eat readily various foods offered to them. They may be obtained in large number and are readily kept in good health so that a considerable number of animals may be used for each test. They may be maintained in good condition and breed actively upon a diet consisting almost wholly of cereal such as oats; animals upon a diet of oats eat meat eagerly.

In many of the experiments rats, which as stock animals had previously received a diet consisting in large part of oats and bread, were given during a short period either (*a*) carbohydrate in the form of rolled oats and cane sugar in lumps, the latter being

eaten in considerable quantities, (*b*) meat in form of pig's heart or beefsteak or (*c*) fat. The fatty diet consisted of beef fat alone, fed during a period of several days before injection of the substance of which the toxicity was tested or beef fat intimately mixed with rolled oats or in some instances cottonseed oil administered by mouth to animals which were receiving the ordinary diet of oats. At the end of a period varying from three to seven days the toxic substance was administered by subcutaneous injection. In some instances the special diet was continued after administration of the toxic substance.

The number of animals which have died in any group of specially dieted animals is an index of variations in toxicity referable to diet. The average duration of life of animals which have died serves as a further indication of variations in toxicity, subordinate in importance to the number of fatalities. Pathological changes in the internal organs have proven an additional index to the influence of diet upon the severity of intoxication.

Chloroform. In the following experiments chloroform was administered to animals which had been subjected to the diets previously enumerated. Chloroform was mixed with two parts of sterile paraffin oil, selected because it is absorbed with difficulty. A preliminary experiment showed that a dose approximately 0.2 c.c. per hundred grams of body weight injected subcutaneously failed to kill, whereas from 0.3 to 0.5 c.c. per hundred grams killed, after four days, 0.6 c.c. after two and 0.7 c.c. within one day. Irregularities in the action of the poison are occasionally seen.

In the series of experiments recorded in Table I animals were given given during four days (1) oats and cane sugar, (2) meat (pig's heart) or (3) fat (beef fat).

TABLE I.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Chloroform per 100 gm.	Oats and sugar.	Meat.	Fat.
0.1 c.c.	—[1]	3	2
0.15 c.c.	3	4	1
0.2 c.c.	7	3	2
0.25 c.c.	—[1]	2	2
0.3 c.c.	4	3	2
Average duration of life	$4\frac{2}{3}+$	3	$1\frac{4}{5}$

[1] Lived.

Animals which received carbohydrates survived, whereas all of those which received meat and fat died. Difference in toxicity is further shown by the average duration of life of animals which survived after the various diets. Microscopic examination of the livers of the animals which died showed that necrosis was scant in animals which had received a carbohydrate diet, implicating one-third or one-fourth of the radius of the liver lobule, whereas in animals which received meat or fat, necrosis affected from two- to three-fifths of the lobules. Necrosis is found in all animals which died within four days after intoxication.

The foregoing experiments suggested that smaller doses of chloroform might demonstrate greater differences referable to diet. In view of the rapid fatality after administration of fat the minimum dose with this diet was placed at 0.025 c.c.; this dose was not administered to animals receiving carbohydrates or meat. After six days on the various diets animals which had received carbohydrates lost an average of 4 gm. each, those on meat maintained their weight and those on fat lost an average of 15 gm. each (Table II).

TABLE II.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Chloroform per 100 gm.	Oats and sugar.	Meat.	Fat.
0.025 c.c.	. . .	. . .	—[1]
0.05 c.c.	—[1]	11	3
0.1 c.c.	10	—[1]	1
0.15 c.c.	—[1]	—[1]	1
0.2 c.c.	—[1]	3	2
0.25 c.c.	—[1]	3	2
Average duration of life	10+	$5\frac{2}{3}$+	$1\frac{4}{5}$

Three times the fatal dose for animals receiving fat (0.05 c.c.) is survived by animals which have received a meat diet, whereas five times this dose is survived by animals which have been fed on starch and sugar. The experiments are in accord with the observations of those who have shown that carbohydrates prevent the disintegration of body proteins. The average duration of life of those which survived furnishes further evidence of the protective action of carbohydrates and the injurious effect of fat. Advanced necrosis of the liver was found in those animals which died

[1] Lived.

after receiving meat and fat, and serves as an index of the severity of intoxication.

Since animals of the foregoing series which received fat exhibited a loss of body-weight, the experiment was repeated by adding fat to a carbohydrate diet. To one group of animals beef fat inseparably mingled with rolled oats was given; to another group which received as much oats as they would eat, cottonseed oil (1 c.c. daily) was administered by mouth. The average body-weight in each of these groups was slightly increased after five days. At the end of this time chloroform was administered (Table III).

TABLE III.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Chloroform per 100 gm.	Oats and sugar.	Meat.	Oats and beef fat.	Oats and cotton-seed oil.
0.05 c.c.	—[1]	2	2	—[1]
0.1 c.c.	—[1]	5	—[1]	2
0.15 c.c.	—[1]	3	2	2
0.2 c.c.	—[1]	3	2	2
0.25 c.c.	—[1]	—[1]	2	4
Average duration of life	...	$4\frac{1}{4}+$	2+	$2\frac{1}{2}+$

The protective action of carbohydrates is conspicuously shown. The difference between the effect of meat alone and of fats combined with carbohydrates is not so great as the difference in the influence of meat and fat alone, the protection afforded by carbohydrates combined with fat being evident. Nevertheless the average duration of life among animals which survived exhibits the dangerous influence of fat.

The fats used in the foregoing experiments have been beef fat which consists of olein, stearin and palmatin and cottonseed oil which is in large part olein. Experiments performed by several Russian observers have shown that cholesterin and foods containing cholesterin produce profound pathological changes in rabbits. Stuckey[2] noted the occurrence of arteriosclerosis in rabbits fed upon egg yolk and brain tissue although no lesions were found in animals which had received pure neutral fats. Chalatow[3] fed rabbits upon egg yolk and brain tissue and noted the accumulation of doubly refractive fat droplets demonstrable in the liver

[1] Lived.
[2] Zent. für allg. Path. und path. Anat., 1912, No. 21.
[3] Virch. Arch., 1912, ccvii, 453.

by means of Nichol's prisms. Within thirty days after the beginning of feeding degenerative changes were found in the liver cells, and there was increase of the interstitial tissue of the organ. Rabbits fed upon egg white, cow's milk, juice of meat, sunflower-seed oil, cod-liver oil and beef fat exhibited no injurious effects. Feeding of egg yolk and brain substance to rats was followed by no accumulation of anisotropic fat in the liver and by no evidence of degenerative change in the hepatic cells. The effect of administration of the two anisotropic lipoids found in egg yolk have been investigated. Wesselkin[1] fed pure lecithin to rabbits and obtained no evidence that it was stored in the liver. Anitschkow[2] maintained that pure cholesterin fed to rabbits causes arteriosclerosis. Chalatow[3] fed cholesterin to rabbits and obtained evidence that it accumulated in the liver, causing in some instances advanced cirrhosis.

Although the experiments just cited have demonstrated no pathological changes produced by cholesterin in omnivorous animals such as the rat, it has seemed not improbable, in view of the increased toxicity to chloroform caused by a fatty diet, that food substances containing cholesterin might influence the toxicity of a substance which causes an hepatic lesion. White rats fed upon brain substance have been given subcutaneously doses of chloroform similar in amount to those previously employed. The animals eat this food eagerly and at least during the period of the experiment maintain their weight. In the following experiment the effect of diets consisting of (*a*) oats and sugar, (*b*) beef fat and (*c*) brain of calf have been compared. The animals have received these diets during six days.

TABLE IV.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Chloroform per 100 gm.	Oats and sugar.	Beef fat.	Calf-brain
0.025 c.c.	—[4]	8	2
0.075 c.c.	—[4]	3	2
0.125 c.c.	4	6	2
0.175 c.c.	—[4]	—[4]	—[4]
0.225 c.c.	—[4]	4	4
Average duration of life	4+	5¼+	2½+

[1] Virch. Arch., 1913, ccxii, 225.
[2] Ziegler's Beiträge, 1913, lvi, 379.
[3] Ziegler's Beiträge, 1913, lvii, 85.
[4] Lived.

The toxicity of chloroform has been greater in animals fed upon brain than in those fed upon fat. The average length of life of animals which received fat was more than twice as great as that of animals which received brain. Egg yolk which contains 35 per cent. of fat including cholesterin and lecithin induces toxicity equal to that found with brain substance.

Phosphorus. The influence of diet upon the toxicity of phosphorus was next tested because the substance exerts a selective action on the liver producing profound injury to the cells of the organ. Fatty degeneration produced by phosphorus is not limited to the cells of the liver for the parenchymatous cells of the kidney, heart muscle, and other organs show a similar change. A 1 per cent. solution of phosphorus in oil (oleum phosphoratum) has been injected subcutaneously. The oil injected with the phosphorus is negligible for the purpose of the experiments since the lethal dose of oil of phosphorus for white rats has proven to be from 0.07 to 0.08 c.c. per hundred grams of body weight. Animals have been given during six days (*a*) oats and cane sugar, (*b*) pig's heart, or (*c*) beef fat; at the end of this time phosphorus had been injected. The special diet has been continued after administration of the substance.

TABLE V.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Oil of phosphorus per 100 gm. of body-weight.	Oats and sugar.	Meat.	Fat
0.05 c.c.	—[1]	11	—[1]
0.06 c.c.	—[1]	4	—[1]
0.07 c.c.	2	4	—[1]
0.08 c.c.	4	4	4
0.09 c.c.	4	2	2
Average duration of life	$3\frac{1}{3}+$	5	3+

In the foregoing experiment pig's heart was given to the animals which received a diet of meat; in another series (Table VI) beefsteak was substituted. In this series the animals received the diet during six days; after phosphorus had been administered, the animals receiving meat and fat were given oats in addition.

[1] Lived.

TABLE VI.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Oil of phosphorus per 100 gm. of body-weight.	Oats and sugar.	Meat.	Fat.
0.05 c.c.	—[1]	4	—[1]
0.06 c.c.	2	3	—[1]
0.07 c.c.	—[1]	3	3
0.08 c.c.	2	3	1
0.09 c.c.	3	1	2
Average duration of life	$2\frac{1}{3}+$	$2\frac{4}{5}$	2+

The effects of diet upon the toxicity of phosphorus differs from those observed with chloroform. Whereas fat has uniformly increased the toxicity of chloroform meat has with equal constancy increased susceptibility to phosphorus. There has been no noteworthy difference in the toxicity of phosphorus with carbohydrate and with fatty diet. The experiments suggest no obvious explanation of these differences in the effects of diet upon chloroform and phosphorus. Certain differences between chloroform and phosphorus may be cited. Chloroform produces necrosis of the centre of each hepatic lobule whereas phosphorus usually produces widespread fatty degeneration which is more intense in the periphery of the lobule. Phosphorus is less destructive to the hepatic cell, but occasionally, when given in large dose and almost constantly, when given to animals which have received a diet of meat, causes widespread necrosis localized especially in the periphery of the lobule. Both substances are soluble in fat but chloroform is absorbed more readily and its toxic action on the liver is far more quickly exhibited. The fatty content of the liver has little influence upon the severity of the lesion which follows the slow deposition of phosphorus in the liver.

Since the experiments which have been recorded demonstrate that lesions of the liver produced by chloroform and phosphorus may be profoundly influenced by diet, experiments have been performed to determine if substances which produce necrosis of the parenchymatous cells of the kidney exhibit similar relations to diet. Potassium chromate and uranium nitrate have been chosen because they have a selective action on the kidney causing

[1] Lived.

necrosis of the renal tubules and leaving the parenchymatous cells of the liver and other organs relatively unaffected. These substances have the further advantage that they have been much used to produce acute nephritis in animals. They cause albuminuria and in the white rat casts are very numerous within the tubules of the kidney.

Potassium Chromate. Potassium chromate has been used in 2.5 per cent. aqueous solution. This has been injected subcutaneously in quantities varying from 0.05 to 0.3 c.c. (0.00125 to 0.0075 gm.). In the following series of experiments animals were given during nineteen days diets consisting of (*a*) oats and sugar, (*b*) pig's heart, (*c*) beef fat. The special diets were continued after administration of potassium chromate.

TABLE VII.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Solution of potassium chromate per 100 gm.	Oats and sugar.	Meat.	Fat.
0.1 c.c.	—[1]	3	6
0.15 c.c.	5	3	3
0.2 c.c.	8	1	3
0.25 c.c.	1	2	2
0.3 c.c.	3	1	1
Average duration of life	$4\frac{1}{4}+$	2	3

Similar results were obtained in another series of experiments in which oats were added to the diets of meat and fat.

TABLE VIII.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Solution of potassium chromate per 100 gm.	Oats and sugar.	Meat.	Egg yolk.
0.05 c.c.	—[2]	2	—[2]
0.1 c.c.	—[2]	2	—[2]
0.15 c.c.	—[2]	4	—[2]
0.2 c.c.	—[2]	5	6
0.25 c.c.	5	3	3
Average duration of life	5+	$3\frac{1}{5}$	$4\frac{1}{4}+$

The experiments indicate that meat increases susceptibility to nephritis caused by potassium chromate, whereas a carbohydrate diet protects the kidney from injury. These conclusions are confirmed by an experiment (Table VIII) in which animals were given

[1] Lived. [2] Lived.

during six days diets consisting of (*a*) oats and sugar, (*b*) meat (beef), and (*c*) boiled egg yolk, which contains 35 per cent. of fat, including cholesterin and lecithin. After injection, animals on diets of meat and of egg yolk received oats in addition.

Uranium Nitrate. Uranium nitrate like potassium chromate causes necrosis of the renal tubules. The physiological studies of Schlayer and Hedinger,[1] Pearce[2] and others have shown that reactions referable to the vascular apparatus of the kidney are not impaired by these substances whereas with the nephritis produced for example, by cantharidin or arsenic, the volume of the kidney does not diminish under the influence of sensory stimuli or adrenalin while diuretics such as caffein or 5 per cent. salt solution do not dilate the bloodvessels and fail to produce diuresis. Uranium nitrate exhibits peculiarities not observed with potassium chromate. At a certain stage of intoxication with uranium nitrate diuretics such as 5 per cent. salt solution, urea, dextrose, etc., cause dilatation of the bloodvessels of the kidney but no increased flow of urine.[3] Well known observations of Richter[4] have demonstrated that uranium nitrate given to rabbits causes subcutaneous edema and accumulation of fluid in the serous cavities when hydremic plethora is produced by the daily administration of water by stomach. Edema is not similarly caused by potassium chromate. A further difference in the action of the two substances has been noted by Christian,[5] who found that uranium nitrate causes a lesion of the glomeruli characterized by the presence of hyaline droplets in the capillary loops and by other changes.

Uranium nitrate has been administered in 0.5 per cent. aqueous solution by subcutaneous injection. In the following series of experiments doses varying from 0.05 to 0.3 c.c. (0.00025 to 0.0015 grams) have been given to animals which during four days had received (*a*) oats and cane sugar, (*b*) beefsteak or (*c*) beef fat; the diets were continued six days after injection of uranium nitrate.

[1] Arch. f. Inn. Med., 1907, xc, 1.
[2] Arch. of Int. Med., 1909, iii, 422.
[3] Schlayer, Hedinger and Takayasu. Arch. f. klin. Med., 1907, xci, 59.
[4] Beit. z. klin. Med., Festsch. f. Senator, 1904.
[5] Jour. of Med. Res., 1913, xxviii, 227.

TABLE IX.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Solution of Uranium nitrate per 100 gm.	Oats and sugar.	Meat (beef).	Beef fat.
0.05 c.c.	—[1]	—[1]	10
0.1 c.c.	6	—[1]	8
0.15 c.c.	7	7	6
0.2 c.c.	9	4	7
0.25 c.c.	—[1]	4	6
0.3 c.c.	10	8	9
Average duration of life	8+	$5\frac{3}{4}$+	$7\frac{2}{3}$

In another series of experiments animals were on various diets only three days, and oats were given to those receiving meat and fat immediately after injection. Differences referable to diet were much diminished, but carbohydrate, meat and fatty diets exhibited the relations noted in the foregoing experiment.

In a third series of experiments uranium nitrate in small doses was given to animals which had received during five days the diets already enumerated; after injection, oats were added to the diet of all animals (Table X). The use of small doses of uranium nitrate in this experiment has made the protective action of carbohydrates very conspicuous.

TABLE X.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Solution of Uranium nitrate per 100 gm.	Oats and sugar.	Meat (beef).	Fat.
0.02 c.c.	—[2]	9	7
0.04 c.c.	—[2]	—[2]	—[2]
0.06 c.c.	7	7	9
0.08 c.c.	—[2]	10	11
0.10 c.c.	—[2]	11	7
Average duration of life	7+	$9\frac{1}{4}$+	$8\frac{1}{2}$+

A carbohydrate diet diminishes the toxicity both of potassium chromate and of uranium nitrate. The toxicity of potassium chromate has been greater after a diet of meat, but the toxicity of uranium nitrate has been somewhat greater after a diet of fat. The pathologic changes produced in the rat by potassium chromate and by uranium nitrate differ. Both substances produce necrosis of tubules in the cortex of the kidney, leaving the glomeruli apparently uninjured. Both substances produce albuminuria, and

[1] Lived.

[2] Lived.

casts are numerous within the convoluted and straight tubules of the kidney. With potassium chromate the convoluted tubules undergo necrosis and with moderately large doses they may be almost uniformly destroyed. Uranium nitrate causes necrosis which is often limited to the cortical striæ and to a narrow zone in the medulla just below the cortex; this distribution appears to be dependent on a selective affinity of the poison for the loops of Henle, which in the early stages of poisoning may exhibit almost uniform necrosis. After administration of relatively large doses of uranium nitrate there is abundant deposition of calcium salts within the dead tubular epithelium.

Discussion. The effect of diet upon the toxicity of two substances, namely, chloroform and phosphorus, capable of causing necrosis of the liver, has been studied and a similar investigation of two substances which cause necrosis of renal tubules, namely, potassium chromate and uranium nitrate, has been made. All of these substances are more toxic for animals which have received a diet of meat than for those which have received a diet consisting in great part of carbohydrate (oats and cane sugar). Upon these diets white rats maintain their weight and remain in good health. Study of the histological changes in animals which have died shows that susceptibility to these poisons is dependent upon the varying extent of necrosis in the liver or kidney induced by diet.

The protective action of carbohydrates, preventing destruction of hepatic or renal cells, is in accord with observations which have shown that a carbohydrate diet prevents the disintegration of body protein. Voit, Rubner and others[1] have shown that carbohydrate given to a healthy individual diminishes the amount of protein needed to maintain nitrogen equilibrium and in starvation reduces the elimination of nitrogen. It is well known that the fever of acute infections is accompanied by increased excretion of nitrogen in the urine due to augmented activity of protein katabolism. Fritz, Voit[2] and Linser and Schmidt[3] found that elevation

[1] For literature to the subject see Lusk. The Science of Nutrition, Philadelphia and London, 1909.

[2] Sitzungsb. d. Gesellsch. f. Morph. u. Physiol. in München, 1895, xi, 120; quoted by Shaffer and Coleman.

[3] Arch. f. klin. Med., 1904, lxxix, 514.

of temperature caused by immersion in warm water was accompanied by increased elimination of nitrogen; they found that it was possible to retard this increased protein katabolism by adding carbohydrate to the food. Shaffer and Coleman[1] have shown that the loss of body-protein which occurs with typhoid fever may be retarded by the use of diets of high caloric value, especially rich in carbohydrate, and if the supply of carbohydrate is sufficient, the loss of nitrogen derived from body-protein may be prevented. Coincident diminution of the excretion of kreatin and of total sulphur indicates that febrile destruction of body-protein is prevented. What relation disintegration of body-protein bears to parenchymatous degeneration of the organs, focal necrosis of the liver and spleen and necrosis affecting the specific lesions of typhoid fever cannot be defined with present knowledge of the subject.

The urine furnishes similar evidence of protein disintegration after administration of chloroform. Strassmann[2] and other observers have shown that anesthesia produced by inhalation of chloroform is followed by increased elimination of urinary nitrogen, sulphuric and phosphoric acids. The experimental studies of Howland and Richards[3] have demonstrated that the increased elimination of nitrogen and sulphur which accompanies intense disintegration of body-protein occurs in association with necrosis of the liver which is the characteristic lesion of delayed chloroform poisoning in all mammals. A similar increase of protein katabolism occurs as the result of phosphorous poisoning (see Ray, McDermott and Lusk[4]).

Necrosis produced by chloroform, phosphorus and similar substances is perhaps the anatomical expression of advanced disintegration of body-protein. Carbohydrate may tend to limit this necrosis by protecting body-protein. Protein diet, in virtue of the specific dynamic action of protein demonstrated by Rubner,[5] increases the activity of metabolism, but how this influences the occurrence of necrosis is not obvious.

The toxicity of two substances, namely chloroform and uranium

[1] Arch. of Intern. Med., 1909, iv, 538.
[2] Strassmann Virchows Arch., 1889, cxv, 1.
[3] Jour. of Exper. Med., 1909, xi, 344.
[4] Amer. Jour. of Physiol., 1899, iii, 139.
[5] Die Gesetze des Emergieverbranchs, 1902.

nitrate, has been greater after a diet of fat than after diets of meat or of carbohydrate. The ready solubility of chloroform in fat suggests the probability that necrosis occurs because chloroform is fixed by the fat present in the cell. The susceptibility of the cells of the kidney and of the liver to necrosis caused by chloroform has a part in the localization of the lesion, for all cells of the body which contain fat do not undergo necrosis. Meyer and Overton maintain that narcosis occurs because a substance soluble in lipoids accumulates in the cells of the central nervous system. They believe that the efficiency of an anesthetic is dependent upon the readiness with which it passes from an aqueous solution into lipoid and may be conveniently expressed by its co-efficient of distribution in oil and water. It is probable that the occurrence of necrosis caused by chloroform is dependent upon two factors: (1) the co-efficient of distribution in fat and water causing the fixation of chloroform, and (2) the injurious action of chloroform upon the protoplasm of the cell, measurable in part by increased activity of protein katabolism.

There is a close analogy between certain human lesions and those produced by the substances which have been employed. Toxemia of pregnancy, acute yellow atrophy of the liver and certain bacterial infections[1] are characterized by necrosis of parenchymatous cells of the liver and not infrequently of the kidney resembling very closely the changes produced by chloroform. In eclampsia the distribution of hepatic necrosis is similar to that which has been caused by phosphorus. Focal necrosis of parenchymatous cells occurs in the liver, spleen and other organs during typhoid fever, malaria, diphtheria, and many other infections. Study of pathological tissues and experimental studies with chloroform and other substances indicate that necrosis of hepatic cells has an important part in the pathogenesis of cirrhosis of the liver. Our experiments performed with four substances which produce localized necrosis indicate that diet may exert an important influence upon the incidence and progress of similar lesions. Increased susceptibility caused by a protein diet and in some

[1] See Mallory, Journal of Med. Research, 1901, vi, 264; and Opie, Ibid., 1904, xii, 147.

instances by fat may have a part in the production of conditions such as toxemia of pregnancy or eclampsia. The experiments suggest that carbohydrate diet may prevent their occurrence or retard their progress.

Conclusions. Diet exerts a profound influence upon the toxicity (tested in the omnivorous white rat) of certain substances, namely, chloroform, phosphorus, potassium chromate and uranium nitrate, which cause necrosis of the parenchymatous cells of the liver or of the kidney. Susceptibility to intoxication with all of these substances is less after a diet rich in carbohydrates than after a diet consisting of meat.

Carbohydrates protect the parenchymatous cells of the liver of the kidneys from necrosis caused by any one of these substances.

Chloroform is much more toxic to animals which have received a diet consisting in great part of fat than to those which have received meat. The solubility of chloroform in fat determines the increased susceptibility of animals which have received fat and stored it in the parenchymatous cells of the liver and kidney.

Susceptibility to intoxication with uranium nitrate which causes nephritis with advanced necrosis of renal tubules is increased by a diet of fat.

DISCUSSION

Dr. S. J. Meltzer: I only want to call attention to the practical side of Dr. Opie's work. It is evident from his results, that chloroform should not be used in diabetes. Furthermore, it may be advisable to feed patients who have to undergo anesthesia on carbohydrates for some days before. It may serve as a protection.

AN EPIDEMIC OF STREPTOCOCCUS SORE THROAT IN JACKSONVILLE, ILLINOIS, WHICH WAS TRACED TO THE MILK OF COWS AFFECTED WITH STREPTOCOCCUS MASTITIS[1]

By JOSEPH A. CAPPS, M.D., AND DAVID J. DAVIS, M.D.
CHICAGO

DURING the past winter there occurred in Jacksonville, Ill., a city of 15,000 people, an unusual number of cases of sore throat. In order to check the spread of the disease twenty-five physicians volunteered their services for the systematic examination of all school children. The epidemic began soon after Thanksgiving Day, 1913, and reached its height in the month of December. In January many persons were on the sick list, but comparatively few new cases were reported. Early in February the number of cases of tonsillitis was not much above the average of other winters. At the request of local physicians the State Food Commission made an investigation of the milk supply, but it reported nothing to indicate a causal relationship between the milk and the epidemic.

Later in January, through the kindness and coöperation of the physicians and the city health commissioner, we were enabled to study the epidemic from a clinical as well as an etiological standpoint. The plan of procedure was as follows:

I. A clinical investigation of cases of sore throat and their relation to the milk supply.

II. Inspection of the cows, dairies, and distributing plants.

III. Bacteriological examinations of throat swabs from infected individuals and of milk from cows showing signs of garget.

[1] The laboratory examinations were made in the Department of Experimental Medicine, University of Illinois, Chicago.

I. Clinical Investigation. 1. Symptomatology.

The outbreak was quite abrupt in the last days of November, rapidly reaching a climax on December 4. (See Chart 1.) After a brief recession came a second prolonged rise in the number of cases that persisted for about two weeks. Thereafter the new cases appeared irregularly.

Altogether 348 cases of sore throat were reported between November 29, 1913, and February 1, 1914.

A definite tonsillitis was described in 217 cases, with appearance of exudate in 104 instances. In addition to a number of cases of true diphtheria with Klebs-Loeffler bacilli, there were 17 cases with an exudate so closely resembling diphtheria that antitoxin was administered. In the latter group Klebs-Loeffler bacilli were not found.

Enlargement of the cervical glands was one of the most constant symptoms, occurring in 192 persons. Among other complications were 5 cases of peritonsillar abscess, 10 of otitis media, 1 of nephritis, 14 of various skin eruptions, not including 4 cases of erysipelas. Rheumatism of an acute or subacute type was described in 16 cases and endocarditis in 6.

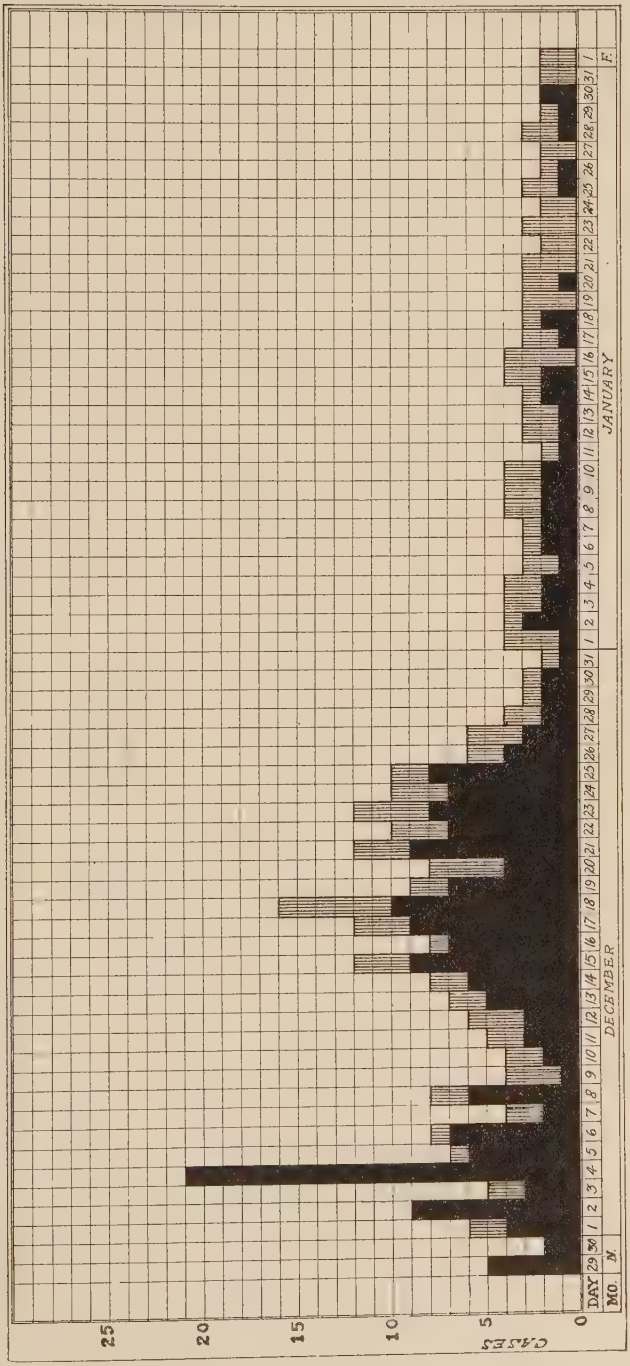
The duration of the disease gives some idea of its unusual severity and persistence. The average period of illness in nearly 200 cases recorded was between nine and ten days.

Three patients died, two from septicemia and one from peritonitis developing soon after tonsillitis.

I. Relation of Sore Throat to Milk. (*a*) In a house to house canvas carried out by Drs. Thompson and Black, a special inquiry was made concerning the use of milk, cream, or ice-cream by the sore throat victims and concerning the dairy supplying each household.

In a total of 913 households investigated, 226 histories of sore throat were obtained. 135 of these cases were using milk, cream, or ice-cream from a dairy that will be called Dairy X. Since Dairy X supplied only 160 out of the 913 households or 17.5 per cent., it is evident that its contribution of 135 out of a total of 226 cases, or 60 per cent., is excessive.

CHART 1



(*b*) There are three large state institutions in Jacksonville, all using milk from their own dairy farms. The physicians in charge furnished us with accurate data upon the incidence of sore throat with the approximate time of onset. Similar information was secured regarding the occupants of a college dormitory and the permanent residents of a hospital. Both of the latter institutions depended upon outside sources for milk.

The accompanying Table I and Chart 2 bring out sharply the high morbidity in the college. Most of the students were attacked between November 29 and December 21. On one day 18 were taken ill. In a total of 200 students 80 or 40 per cent. were victims.

TABLE I.—SHOWING THE COMPARATIVE MORBIDITY IN THE SEVERAL INSTITUTIONS AND THE MILK SUPPLY OF SAME

Institution.	No. residents.	Number cases sore throat.	Per cent. affected.	Dairy.
Blind	198	5	2.5	Own
Deaf and dumb	478	34	7.1	Own
Insane	1725	1	.05	Own
College	200	80	40.0	X
Hospital	50	2	4.0	A

The college was supplied with milk and cream by the aforementioned Dairy X.

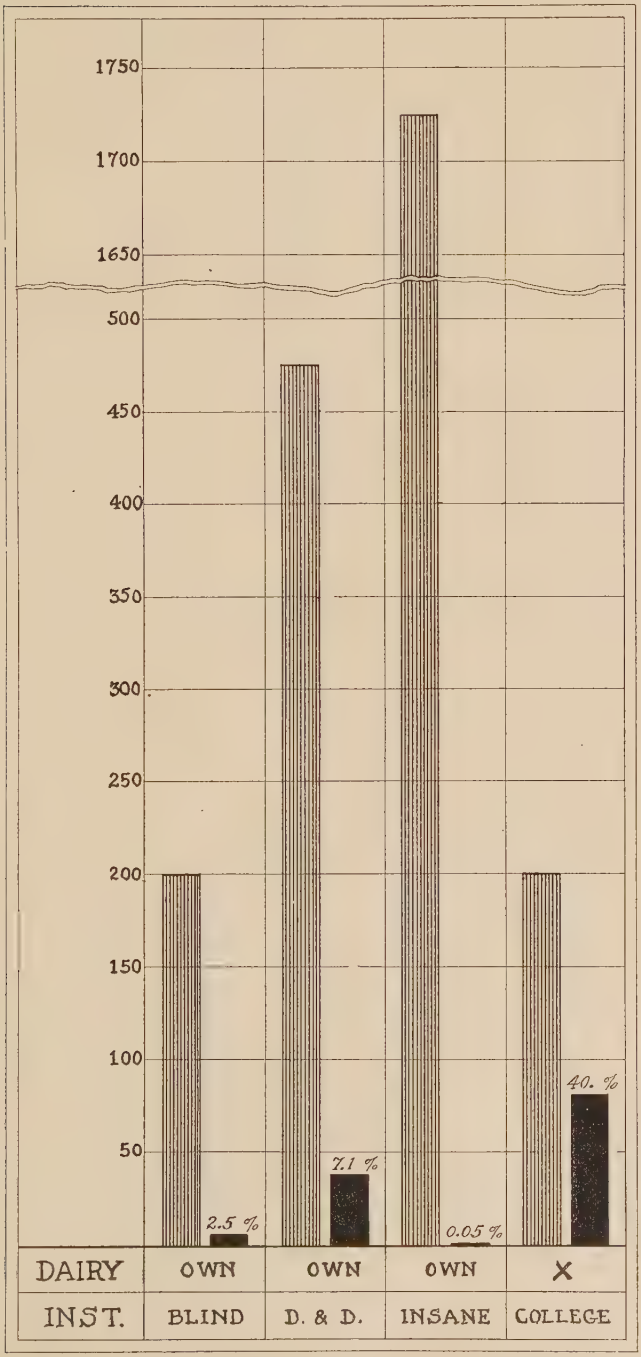
The morbidity in the four other institutions varied from less than 1 per cent. to 7.1 per cent., averaging 1.7 per cent.

An interesting situation at the Insane Hospital should be noted. Twenty-five attendants and other employees, of a total of 220, consulted the house physician for sore throat. These persons often had occasion to eat and drink outside the hospital premises. In spite of close daily contact of these attendants with their charges, only one of the 1725 patients contracted sore throat during December and January. The element of contagion from one person to another seems to have been negligible.

Again it may be emphasized that the morbidity of sore throat in the college supplied by Dairy X was over twenty times that of the four other institutions supplied by other dairies.

When a summary is made of 7416 individuals investigated both in households and institutions, we find that approximately 1000

CHART 2


1750
1700
1650
500
450
400
350
300
250
200
150
100
50
2.5 %
7.1 %
0.05 %
40. %
DAIRY
OWN
OWN
OWN
X
INST.
BLIND
D. & D.
INSANE
COLLEGE

or 13.50 per cent. are customers of Dairy X. Of the total of 348 cases of sore throat 215 or 62 per cent. are users of Dairy X milk. (See Table II, and Chart 3.)

TABLE II

Total number of individuals investigated	7416.0
Number of individuals using milk of Dairy X	1000.0
Number of individuals using milk of other dairies	6416.0
Total number of cases of sore throat	348.0
Cases of sore throat using milk of Dairy X	215.0
Cases of sore throat using milk of other dairies	133.0
Percentage of individuals supplied by Dairy X	13.5
Percentage of cases of sore throat using milk of Dairy X	62.0

Furthermore, among the 6416 customers of other dairies, 133, or 2.1 per cent., developed sore throat, while among the 1000 customers of Dairy X, 215, or 21.5 per cent., contracted the disease. (See Chart 3.)

II. INSPECTION OF COWS. For the inspection of the cows we were fortunate in securing the services of Mr. Krüger, an experienced dairy inspector in the Chicago Health Department.

In previous epidemics of septic sore throat the dairy investigation has been limited to those herds supplying milk that is under suspicion. Such a procedure fails to give information of the prevalence of garget in other herds as a basis of comparison. Furthermore, it is important to know if streptococcus mastitis may exist without being pathogenic to man.

For these reasons the scope of dairy inspection was broadened so as to include all the cows in the larger dairies supplying the city.

On each farm it was ascertained if any members of the farmer's household had been afflicted with sore throat. The cows were examined carefully for caked bag or garget. Whenever garget was discovered, samples of the milk were taken separately in large tubes from each quarter of the bag under aseptic precautions, tightly sealed and forwarded at once to the laboratory of the University of Illinois in Chicago.

In this manner inspection was made of 416 cows in 38 different farms. (See Table III.)

CHART 3

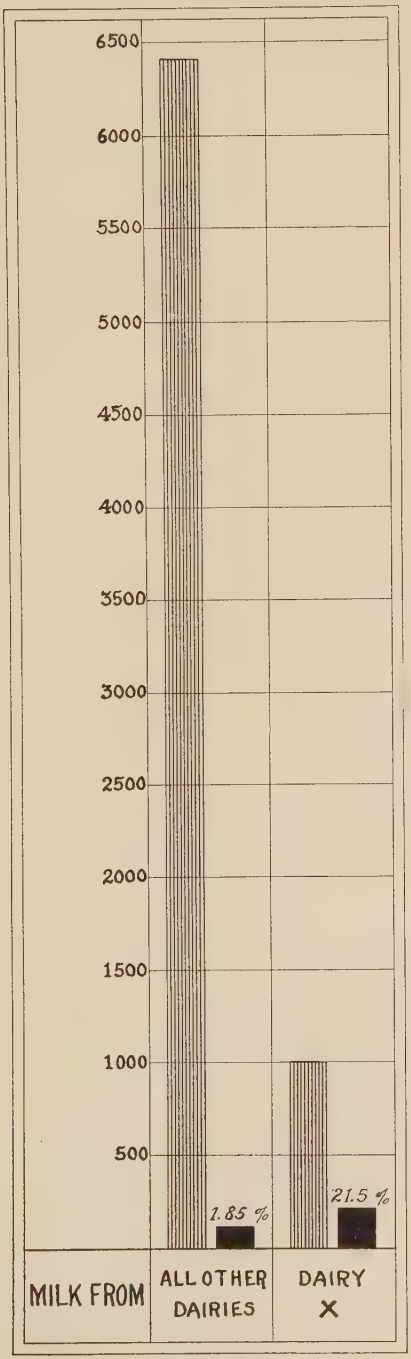

6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
1.85 %
21.5 %
MILK FROM
ALL OTHER DAIRIES
DAIRY X

TABLE III.—INSPECTION OF COWS AND DAIRIES

Dairy.	No. of cows.	Sore throat on farms.	Infected cows.	Infecting organism.	Remarks.
1	45	0	1	Staphylococcus albus.	Cow hurt on wire fence.
2	9	0	1	Staphylococcus albus.	Milk very yellow in color.
3	13	Girl, December 15 2 weeks duration.	1 late in November	Hemolytic streptococcus.	Milk supplied to Dairy X.
4	13	0	1	Hemolytic streptococcus.	Milk supplied to Dairy X.
5	4	0	1	Staphylococcus albus and aureus, Streptococcus viridans.	
6	9	0	0		
7	28	0	0		
8	22	0	0		
9	11	0	0		
10	11	Boy, January 26.	0		
11	5	0	0		
12	6	0	0		
13	12	0	0		
14	2	2 boys, January 14.	0	.....	Use X Dairy milk.
15	12	0	0		
16	6	0	0		
17	4	0	0		
18	14	0	1 suspicious	No organism found.	
19	6	0	0		
20	5	0	0		
21	7	0	0		
22	6	0	0		
23	5	0	0		
24	7	0	0		
25	4	1 child, January 6.	0		
26	4	0	0		
27	9	0	0		
28	6	0	0		
29	13	0	0		
30	10	0	1 old case not examined.		
31	7	0	0		
32	34	0	0		
33	15	1 case January 1 to 14; duration 10 days.	0	.....	Milk to Dairy X.
34	17	0	0		
35	16	1 case December 25 duration 10 days.	0	.....	Milk to Dairy X.
36	7	0	1 November 24.	Staphylococcus albus.	Milk to Dairy X.
37	6	0	2 January 1 to 14; December 20 to 13.	Staphylococcus albus and aureus.	
38	6	0	1	Staphylococcus albus. Fine bacillus.	

Eleven cows were found with garget, which is about 2.6 per cent. As the prevalence of garget in the Chicago epidemic was 4.6 per cent., we are not warranted in assuming that this disease was unusually common in the cows near Jacksonville. All of the cows with mastitis were placed under quarantine by the milk committee of the local medical society. Two of the eleven cases were caused by streptococci. These it will be observed, came from farms that delivered milk to Dairy X.

In the farmers' families, six cases of sore throat were reported. None of them were milkers. All appeared after the outbreak of the epidemic. We think it is reasonable to assume, therefore, that these cases had no causal relation to the epidemic. Careful investigation, furthermore, failed to reveal any cases of sore throat about the dairies or distributing plants which could be brought into relation in any way with the outbreak of the epidemic. We thoroughly appreciate the importance of human "carriers" as possible sources for the infecting streptococci, but we could obtain no evidence that such persons played any role in the epidemic.

The Plant of Dairy X. Dairy X obtained its milk and cream from many farmers. The company sells milk and butter and a great deal of cream. It furnishes cream to the largest manufacturer and distributor of ice-cream in the city. At the creamery plant is a pasteurizing apparatus which subjects the milk to a temperature of 140° to 145° for a short and entirely inadequate period. *Cream was not pasteurized at all during the winter.* None of the employees at the plant suffered from tonsillitis during the winter.

III. Bacteriological Investigation. The clinical symptoms, the general course of the disease, the character of the epidemic, and its evident connection with the milk supply would suggest at once that we have to do with a streptococcus infection, similar in character to the Chicago, Boston, and Baltimore epidemics. Furthermore, the reports of throat examinations made by local physicians indicated the presence of numerous diplococci and streptococci in the smears obtained from the patients. Diphtheria was suspected often in these cases, but the cultures nearly always gave negative results for B. diphtheriæ, thereby showing that

the infection was due to some other germ, probably streptococcus.

Unfortunately owing to the fact that the epidemic was on the decline when the study began, not as many cultures were obtained as we wished. However, in six typical cases, streptococci were found as the predominating organism in smears and cultures of these swabs in large numbers. In one case an abscess occurred in the glands of the neck from which a pure growth of this organism resulted. The characteristics of these organisms isolated from throats will be considered later in connection with a discussion of the organism obtained from the milk.

As already stated, in an inspection of 416 cows from dairies about Jacksonville, eleven animals were found with diseased udders and samples of milk were obtained from each for bacteriological examination. For this purpose the teats were cleansed and the first milk rejected. The milk was then collected directly in sterile test-tubes and immediately sent to the laboratory for examination. The results are presented in tabular form. (See Table III.) Two cows were found on different farms, having streptococcus mastitis. The organisms were present in large numbers in the milk, together with many leukocytes. The presence of the pus was immediately detected in the form of a slimy sediment in the centrifuge tube, and a small amount of blood was present in one of the samples. In one cow two quarters were infected, in the other animal all four quarters were involved. Staphylococci were found in the milk from 7 of the cows. In one was a fine small Gram-negative bacillus in large numbers and in another animal was obtained in smears and cultures a hemolytic streptococcus similar in many respects to the streptococcus viridans, but without definite pathogenic properties for animals.

The properties of the streptococci isolated from the throats and from the diseased cows have been studied.

Of the six strains isolated from the throats four grow like the streptococcus[1] isolated during the Chicago epidemic two years ago. The other two do not show these properties as distinctly

[1] Jour. Amer. Med. Assoc., 1912, vol. lviii, p. 1852.

and closely resemble the ordinary hemolytic streptococcus. The two strains isolated from the udders of the cows showed capsules, a narrow zone of hemolysis and were pathogenic for rabbits in doses of one to two slant agar tubes producing multiple arthritis in three to four days. They clearly belong to the Streptococcus pyogenes group and correspond to the epidemic streptococcus found in the throats. In Table IV are given the properties of

TABLE IV.—PROPERTIES OF EPIDEMIC STREPTOCOCCI FROM THROATS AND FROM COWS

No.	Origin of culture.	Hemolysis.	Capsule.	Pathogenic for rabbits.	Dextrose.	Saccharin.	Lactose.	Mannite.	Maltose.	Inulin.	Raffinose.
1.	Human I (Jacksonville)	+	+	+	+	+	+	0	+	0	0
2.	Human II (Jacksonville)	+	+	+	+	+	+	0	+	0	0
3.	Human III (Jacksonville)	+	+	+	+	+	+	0	+	0	0
4.	Human IV (Jacksonville	+	+	+	+	+	+	+	+	0	0
5.	Human V (Jacksonville)	+	0	+	+	+	0	0	+	0	0
6.	Human VI (Jacksonville	+	+	+	+	+	+	0	+	0	0
7.	Human VII (Jacksonville)	+	0	+	+	+	+	0	+	0	0
8.	Bovine I (Jacksonville) Dairy No. 3	+	+	+	+	+	+	0	+	0	0
9.	Bovine II (Jacksonville) Dairy No. 4	+	+	+	+	+	+	0	+	0	0
10.	Bovine III (Jacksonville) Dairy No. 5	0	0	0	+	0	+	0	+	0	0
11.	Epidemic streptococcus Human, Chicago epidemic	+	+	+	+	+	+	0	+	0	0
12.	Epidemic streptococcus Bovine, Chicago epidemic	+	0±	+	+	+	+	0	+	0	0

these various streptococci and their reactions on different sugars. The organisms from the cows and from the throats agree in practically every detail. For comparison, Nos. 11 and 12 are typical streptococci isolated two years ago during the Chicago milk epidemic of sore throat. It will be seen that there is no essential difference in their properties from the organisms isolated in the Jacksonville epidemic.

VIABILITY OF GERMS IN MILK PRODUCTS. During the study of this epidemic questions were frequently asked as to the infectivity of sour milk, buttermilk, butter, cream, ice-cream, etc. A somewhat detailed study is being made of this problem

which will be reported in detail. Here only some general statements will be made. During the process of souring hemolytic and epidemic cocci are gradually killed, as can readily be shown by making plates at regular intervals. These organisms are killed in three hours or less by the acidity of sour milk (forty-eight hours after curdling) and buttermilk. They die out in ordinary butter in the course of a few days. This is also due to the acidity for in neutral butter they live for a long time. In ice-cream streptococci remain alive for at least three weeks and without any appreciable diminution in number of virulence. Ice-cream would seem to be the medium *par excellence* for the transmission and preservation of dangerous streptococci. Separator cream contains somewhat more organisms than the whole milk, and the skim milk contains less. The sediment, of course, contains large numbers. These facts are explained thus: the fat particles as they ascend carry with them mechanically a certain number of streptococci and other germs. On the other hand many organisms are thrown down by centrifugation. In this way the number of organisms in the cream and the sediment is increased while in the skim milk there is a decrease. Hemolytic and epidemic streptococci ordinarily do not multiply to any extent at 20° C. (68° F.). At 27° C. (80° C.) there is little or no multiplication during the first few hours in milk (sterile or commercial), but at the end of twenty-four hours, in sterile litmus milk there is considerable increase. In ordinary commercial milk containing the common milk bacteria this multiplication is largely inhibited by the growth of these contaminating germs. Therefore, it is probable that under few conditions met with in the ordinary handling of milk can any appreciable increase of hemolytic or epidemic streptococci occur.

Even under most favorable temperature conditions multiplication of these streptococci in sterile milk does not begin for two to three hours. It is, therefore, impossible for any appreciable increase of the dangerous streptococci to occur during the short time while the temperature of milk is being raised and lowered in the process of pasteurization.

SUMMARY

1. The epidemic of septic sore throat began abruptly, was most active in the first four weeks, and gradually subsided after about eight weeks.

2. There were 348 cases of sore throat, most of them complicated by enlargement of the cervical glands and many by a marked exudate. Cultures from a number of throats showed a hemolytic streptococcus.

3. In a canvass of 913 households, 60 per cent. of the cases of sore throat used milk or cream from Dairy X, although this dairy supplied only 17.5 per cent. of the households.

4. The morbidity rate in one institution supplied by Dairy X was 40 per cent., in four other institutions supplied by other dairies it averaged 1.7 per cent.

5. Among the 1000 customers of Dairy X, 215 or 21.5 per cent. developed sore throat, whereas among the 6416 customers of other diaries 133 or 2.1 per cent. developed the disease.

6. As a result of a systematic inspection of 416 cows on 38 dairy farms, 11 cows with garget were found.

7. Bacteriological examinations revealed hemolytic streptococci in the milk of 2 of these diseased cows. The milk of both of these cows was distributed by Dairy X.

8. As Dairy X did not pasteurize the cream at all and the milk very inadequately, we may conclude that the streptococci originating in the bovine mastitis were responsible for the epidemic.

9. A study of these streptococci under varying conditions in the milk shows these characteristics:

(*a*) They do not appreciably multiply at room or warm temperature because of the inhibiting influences of other milk bacteria.

(*b*) They are soon killed by the acidity of sour milk or buttermilk.

(*c*) They die out in ordinary butter in a few days, because of acid formation.

(*d*) They live in ice-cream for at least three weeks without appreciable loss of numbers or virulence. Ice-cream, therefore, is

a peculiarly favorable medium for the dissemination of the germs.

10. Because of the extensive distribution of ice-cream, manufactured from the Dairy X cream, we suspect that ice-cream played an important role as a carrier.

DISCUSSION

Dr. George M. Kober: I should like to say a few words in reference to Dr. Capps' paper, whose contribution is of great interest to the student of preventive medicine.

In 1894, when I made a collection of milk-borne epidemics, I was especially impressed with the studies made in England by W. H. Power, in 1885, in regard to epidemics of scarlet fever, which were traced to a particular farm at Herndon, but he could discover no sign of scarlet fever, at or near the dairy; upon examination of the cows, however, some of them were found to be suffering from an inflammatory condition of the teats and udder of the animal, and from various circumstances, he inclined to the belief of the bovine origin of scarlet fever. Dr. Klein was requested to make an investigation and found certain micrococci in the diseased tissues of these cows, which he believed to be the etiological factor of scarlet fever. The subject led to a controversy, and engendered considerable heartburnings among British pathologists. In analyzing the situation I concluded and ventured to express the opinion in 1895, that the cases in question were not true cases of scarlet fever, but typical instances of either staphylococcus or streptococcus infections. I had seen quite a number of cases of streptococcus sore throat in which there was an eruption of the nature of scarlet fever, and when we consider that toxins may and do produce a scarlatinous exanthem, I felt warranted in believing that in this instance and in all epidemics of so-called scarlet fever and diphtheria, which were traced to milk from cows suffering with some inflammatory lesions of the udder, or from puerperal fever, we had to deal with typical instances of a streptococcus or staphylococcus infection, and it is often difficult to differentiate clinically such attacks from true diphtheria and scarlet fever. In August, 1897, Grey Edwards published in the *British Med. Jour.*, vol ii, p. 340, cases of follicular tonsillitis, in which the Staphylococcus pyogenes aureus and albus, and the Streptococcus pyogenes (short form) were not only found in the milk of suspected animals, but also in the sweeping culture from the throat. In our present

state of knowledge it seems to me that nothing short of pasteurization will confer immunity from these infections and other milk-borne diseases.

Dr. R. C. Cabot: I would like to ask Dr. Capps what sort of an eruption these patients had.

Dr. Capps (closing): Many of the eruptions were erythematous. There were one or two cases in which there was a resemblance to scarlet fever. Four of the cases were described and diagnosed as erysipelas by good clinicians.

PATENT DUCTUS ARTERIOSUS WITH ACUTE INFECTIVE PULMONARY ENDARTERITIS

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AND
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Cases presenting the signs of persistent ductus Botalli are comparatively rare. The clinical diagnosis of this case, confirmed at autopsy, and the very interesting, if not altogether unique, pathological condition found, justify placing it on record.

The patient was a fairly well developed girl, aged nineteen years, who, while never very strong, had never suffered any serious illness save that of scarlet fever in childhood. In the middle of August, 1913, chills, lassitude, weakness and diarrhea set in, symptoms of a general infection resembling that of typhoid fever. A few signs attracted one's attention to the base of the right lung where the percussion note was slightly impaired, and where moist rales were occasionally heard. The course of the case, the temperature, the absence of typical spots and of the Widal reaction, the white cell count of 17,000 with Gram-positive diplococci in the blood culture, proved the case one of septicemia other than that of typhoid fever.

The great vessels at the base of the heart were thought to contain a focus of infection about which so much interest centres. The heart itself was enlarged to the left, and the dulness noted was wider than usual on the left, even in the second and third interspaces (Fig. 1, Radiograph). A faint systolic thrill was occasionally felt over the pulmonary area, where the second sound could be felt sharply accentuated. Here, too, the harsh rumbling continuous murmur, occupying the whole of the cardiac cycle, was best heard. The murmur increased in intensity with systole and diminished in diastole. It was transmitted upward, and to the left, but was not heard behind (Franck's sign). The cardiac signs gave no indication of mitral or other valvular disease.

After an illness of two months, quite characteristic of septicemia, the patient died.

The autopsy, which was performed by Dr. O. C. Gruner, showed the following remarkable combination: *Patent ductus arteriosus*

Fig. 1.—Radiogram from a case of patent ductus arteriosus. The second space marked along the left border of the heart is noted here as unusually prominent—the dilated pulmonary artery.

with acute infective endarteritis of its pulmonary end, and of the pulmonary artery adjacent, of pneumococcus origin, with formation of mycotic aneurysm of the main pulmonary trunk, and blocking of its left branch by a thrombotic mass. Dilatation of the pulmonary artery,

hypoplasia, and coarctation of the aorta. Slight hypertrophy and marked dilatation of the right ventricle of the heart, the endocardium healthy, no cardiac anomaly. Multiple septic embolism of both lungs, with infarction and abscess formation, bilateral acute fibrinous pleurisy. Calcification of mediastinal glands about pulmonary end of ductus, with acute lymphadenitis of peribronchial and periaortic glands. Cloudy swelling of kidneys, fatty degeneration of liver, infarct of spleen. Pneumococci in vegetations on pulmonary artery and in embolic abscesses in lungs.

The interest of the case centres in the condition of the great arterial trunks and lungs. The main trunk of the right pulmonary artery was clear, but several of its branches were occluded by white septic thrombi, and the right lung was riddled with septic infarcts and embolic abscesses of old and recent date. The peribronchial lymph glands about the hilum of the lungs were enlarged and succulent, markedly inflamed. In the left lung the thrombotic process extended along the main branches of the pulmonary artery for some distance, completely occluding these. The apex of the upper lobe was occupied by a single small gray septic infarct, and the vessel leading to this area was blocked by the grayish white thrombotic mass.

The aorta was healthy throughout, but it diminished from a circumference of 6 cm. at its origin to 5 cm. beyond the left subclavian, narrowing still further to a circumference of 4 cm. in its descending portion. It presented, at a point 5.5 cm. above the aortic cusps, a little beyond the origin of the left subclavian artery, and on the opposite wall, a round orifice admitting a penholder with sharply defined lower border which led into a canal 0.75 cm. long (patent ductus arteriosus), communicating with the pulmonary artery about 2.5 cm. above the pulmonary valves.

The pulmonary artery was dilated, and was laid open from behind (Fig. 2). Its lumen was occupied by a large moist reddish gray thrombus of smooth lobulated contour, which lay across the pulmonary orifice of the ductus, covering but not occluding this. The clot was roughly pyramidal in shape, its broad base lying vertically in the main lumen of the artery, and its apex projecting into and blocking the branch supplying the left lung, the right pulmonary, and the right half of the main lumen of the artery remaining free;

a ragged fibrinous prolongation of the thrombus was sent downward also to within 1 cm. of the pulmonary valves. The main portion of the thrombus was attached to the subjacent arterial wall by a broad base 2 x 4 cm. in diameter, the lower border of which lay 2 cm. above the pulmonary valves. On raising the mass it was found to spring from an ovoid area of vegetations lying on the right anterior wall of the artery. The pulmonary orifice of the ductus

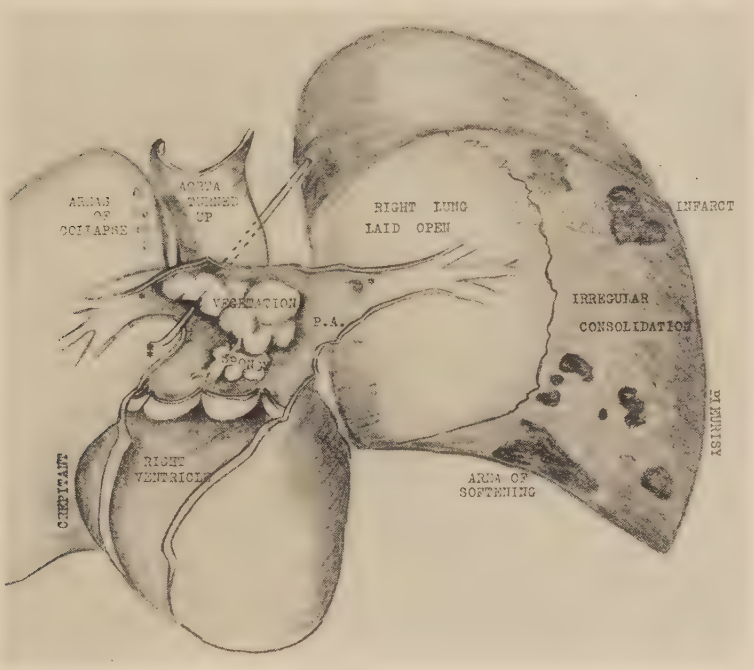

FIG. 2.—Looking from behind. * Orifices of pulmonary arteries. ‡ Probe introduced through small patent ductus arteriosus into aorta.

occupied the centre of this area and was evidently the starting-point of the process, for its edges were surmounted by a ring of firm fibrinous vegetations (one over 1 cm. long), which invaded its lumen for a short distance. The remaining four-fifths of the canal on the side of the aorta appeared smooth and healthy, to the naked eye, but proved on microscopic examination, to be also diseased. Just to the right of the pulmonary orifice of the ductus, the inflammatory process had been most intense, and had resulted in a complete

necrosis of the arterial wall, a mycotic aneurysm resulting. Section through the margin of this necrosed area showed the destructive inflammatory process spreading both without the vessel wall and within its lumen, the tissue of the relatively intact arterial coat showing up sharply between two necrotic zones. This appearance was further confirmed by microscopic investigation. At the outer margin of the diseased area in the pulmonary artery the thrombotic material could be lifted away, leaving an apparently intact intima, while in the neighborhood of the ductus it was densely adherent and incorporated with the necrosed arterial wall. Closely embracing the outer surface of the upper wall of the pulmonary end of the ductus and incorporated with its coats was a calcified mass of glandular tissue, which must have formed an unyielding structure at this point, thus narrowing the lumen and possibly furnishing a seat of maximum strain, which may have given origin to the disease within. A second still larger calcareous mass, the size of an almond, lay in the angle formed by the lower wall of the ductus and the pulmonary artery.

Remarks. The diagnosis of patent ductus arteriosus was made during life from the characteristic physical signs:

(*a*) Dulness in the upper spaces to the left of the sternum.

(*b*) A thrill.

(*c*) The accentuated pulmonic sound.

(*d*) The radiograph showing a shadow over the pulmonary area due to increased volume of the pulmonary artery.

(*e*) A continuous systolic-diastolic murmur at the base of the heart, increasing in systole and transmitted up and to the left.

Of all these signs it would seem from the literature and the writers' experience that the last mentioned is deserving of first place as indicating the anomaly under discussion, although there is at present a tendency to regard the fluoroscopic method as having greater value in the diagnosis. The importance of the radiograph seems indeed to us to lie chiefly in its confirmatory value in the presence of other characteristic physical signs.

The present case is of interest as being one of the very few reported in which the characteristic *x*-ray shadow observed during life has been proved at autopsy to be due to the dilated pulmonary artery in association with patent ductus arteriosus. An autopsy was ob-

tained also in Mead's[1] case, diagnosed by Thayer, in which a "continuous machinery murmur" with systolic accentuation was associated on the fluoroscopic examination with "a localized bulging of the left side of the base of the heart in close juxtaposition with the descending arch of the aorta." Among Goodman's[2] series of 34 cases of patent ductus arteriosus with autopsy findings, in only one had the fluoroscopic examination been made, while in the 37 cases collected by him in which the clinical diagnosis only had been established, the *x*-ray shadow over the dilated pulmonary artery was noted in 17.

The diagnosis of an infective pulmonary endarteritis about the orifice of the patent ductus was also here confidently suggested from a knowlege of the occurrence of such cases as recorded in the literature, and the fact that there was present in this case, septicemia, unassociated with any known focus of infection, or clinical signs of endocardial involvement. Ten such cases, and probably more, have been reported, but in all these the disease of the pulmonary artery was associated with a malignant endocarditis of one or more valves. Our case is, as far as we know, unique in the literature, in that there was here no involvement of the heart, both valvular and mural endocardium being free from any trace of disease.

This fact adds greatly to the pathological interest of the case, which centres about the origin of the infective process in the pulmonary artery, here plainly shown to be due, not to an extension either by contiguity or continuity of an inflammatory focus originating in the heart, but to a primary lesion of the arterial wall itself, adjacent to, or at, the ductus orifice, or within its canal. The causation must, therefore, have been the direct invasion of the wall by an infection carried either through its vasa vasorum or through the blood-stream in the main arterial trunk. We may therefore conclude that we are dealing here with a local process in the pulmonary artery, and the question as to its origin is a threefold one. Was the infection embolic in the vasa vasorum? Or was it carried in the main blood-stream and lodged at the seat of maximum strain and lowered resistance? Or was the process in the first place

[1] Jour. Amer. Med. Assoc., 1910, vol. lv, p. 2205.
[2] Univ. Penna. Med. Bull., 1910, vol. xxiii, p. 509.

a mechanical one, the strain upon the pulmonary end of the ductus resulting in the formation of minute tears in the intima followed by a

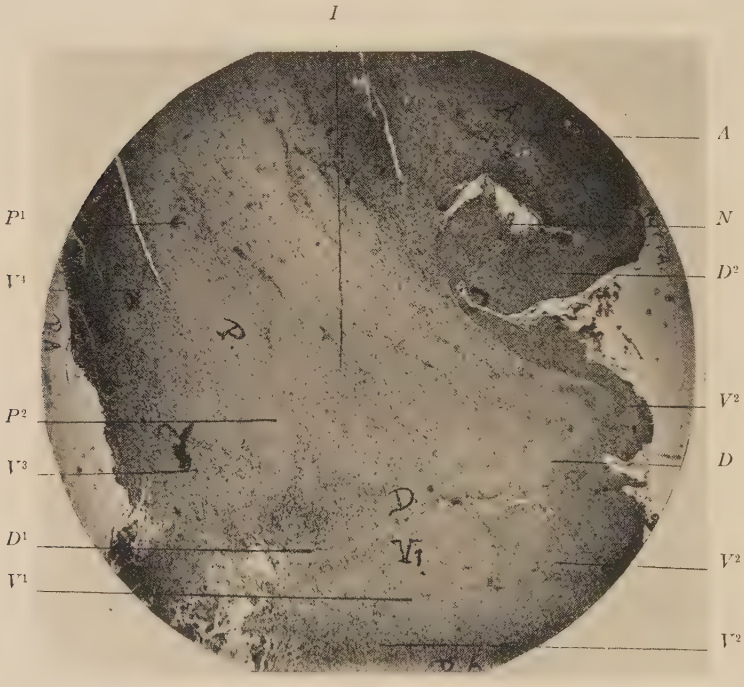

FIG. 3.—Section from rectangular block taken through entire length of ductus and adjacent portions of aorta and pulmonary artery. (Stained H. and E. Leitz obj. No. 2.) *D*, free margin of patent ductus, necrosed and inflamed in all its coats, its elastic tissue in large part destroyed; D^1, angle of junction with pulmonary artery (seat of initial lesion); D^2, angle of junction with aorta (advanced necrosis). *A*, wall of aorta adjacent to ductus, healthy throughout. *P*, wall of pulmonary artery; P^1, wall of pulmonary artery at a distance from ductus, healthy; P^2, wall of pulmonary artery in immediate neighborhood of ductus, intima superficially necrosed, deeper coats healthy. *V*, huge vegetation surmounting necrosed wall of ductus in its entire length and extending over wall of pulmonary artery immediately adjacent; V^1, young, newly vascularized granulation tissue at angle of junction of ductus with pulmonary artery (initial lesion); V^2, unorganized thrombotic mass covering necrosed wall of ductus from angle of junction with aorta (D^2), extending over mass of granulation tissue (V^1) at angle of junction with pulmonary artery and continuous with thrombotic mass here; V^3, unorganized thrombotic mass overlying and incorporated with necrosed pulmonary intima immediately adjacent to ductus; V^4, unorganized thrombotic mass overlying healthy pulmonary artery at a distance from ductus (P^1), not incorporated with it. *N*, area of acute recent extensive necrosis at junction of ductus with healthy aorta (D^2). *I*, area of acute inflammatory cell infiltration in cellular tissue between outer walls of aorta, pulmonary artery and ductus, proceeding from the latter vessel. *Aorta*, lumen of aorta. *P.A.*, lumen of pulmonary artery; *D.A.*, lumen of ductus arteriosus.

simple thrombosis at the seat of injury and secondary infection of this by the circulating organisms?

The reply to these questions is to be found, we think, in the study of the vessel wall in and about the seat of the initial lesion.

For this purpose the following sections were made: (*a*) A large thin slice was cut from the upper wall of the ductus, from end to end of its canal. The rectangular block thus obtained presented a section of the wall of the ductus in its entire length, with the adjacent portions of the aorta and pulmonary artery at either end, and the intervening tissue external to and between the outer surfaces of these vessels (Fig. 3); (*b*) a slice through the opposite margin of the ductus in the pulmonary artery involving the angle of junction of these two structures; (*c*) sections from various parts of the diseased area in the pulmonary artery at some distance from the ductus, including (*d*) the immediate neighborhood of the mycotic aneurysm, where the destructive process was most intense; (*e*) a section from the wall of the apparently healthy pulmonary artery at some distance from the diseased focus. The material was studied with the help of the elastic tissue, Gram-Weigert, and hematoxylin-eosin stains.

(*a*) The large rectangular block containing the ductus and adjacent structures was sectioned *in toto* (Fig. 3), and revealed the *earliest seat of disease to be at the pulmonary end of the ductus,* which was the only point at which organization was manifest, the process everywhere else both in the ductus and pulmonary artery being of a rapidly progressive and highly destructive character. At this point *the angle formed by the walls of the ductus and pulmonary artery was surmounted by a large mass of vegetations which consisted of well organized young granulation tissue very cellular in character, and containing many newly formed bloodvessels* (Fig. 3, V. 1), evidencing a considerable duration. These vegetations were surmounted by a layer of recent thrombotic material which extended also along the wall of the pulmonary artery for a short distance, being at first merged with this, and further out simply superimposed upon it. In the immediate neighborhood of the ductus the pulmonary intima showed superficial inflammation and its endothelium was necrosed, but its deeper structures including its entire media were even here intact, and beyond the thrombotic exudate the wall of this artery was healthy and free from any evidence of disease.

Following the ductus inward toward its aortic end (Fig. 3, D^2) its entire wall was found to be extensively diseased by a recent highly destructive process, its inner coat necrosed, replaced, and covered by thrombotic exudate, and the elastic tissue of its deeper layers lying in broken shreds and islands in the midst of inflammatory exudate and debris. An acutely destructive and very recent process (Fig. 3, N) involved the extreme end of the canal immediately before its junction with the aorta, where it was hollowed into a deep bay in the depths of which lay masses of fibrin and beds of leukocytes and other inflammatory cells. The process was here sharply delimited by the aorta, whose endothelium, intima and media showed no evidence of acute inflammation, the only change noted being a thickening of the walls of its vasa vasorum as from raised peripheral pressure. In the tissue external to the ductus wall, however, and lying between aorta and pulmonary artery (Fig. 3, I) the same acute process had spread, a recent intense inflammation, suppurative and destructive in character, existing.

No pneumococci were present in this section either in the vessel wall or vegetations, or in the recent thrombotic material. The remarkable feature of this whole section is the localization of all organization to the pulmonary end of the ductus, and the limitation of the recent destructive process to this canal and its environs, and the absolute freedom of the deeper layers of the pulmonary artery or aorta from any local foci of disease that could suggest an embolic orgin through the vasa vasorum. *The infective process is here undoubtedly and distinctively superficial in its origin* in relation to the inner surface of the arterial wall.

(*b*) The section through the orifice of the ductus and the adjacent pulmonary artery, on the side opposite to the rectangular block removed, showed an identical process to that occurring here. The ductus wall was extensively destroyed, and the adjacent pulmonary artery relatively intact, but with an inflamed intima, while superimposed on the angle formed by the two structures was a large vegetation, which consisted of organizing tissue at its base, and superficially of a thrombotic mass, in which lay embedded numerous pneumococci.

(*c*) The sections from the diseased area in the pulmonary artery at a distance from the ductus showed everywhere an extremely destructive, thrombotic process, rapidly advancing and of recent date, which (*d*) at the site of the myocotic aneurysm had entirely destroyed the arterial wall, including the elastic tissue of the media, but elsewhere had shown itself superficial to this structure extending both over the inner surface of the artery and burrowing outside of its coats, leaving the wall itself practically intact between two necrotic thrombotic zones. Here also the *media* showed little change, there were no embolic foci, while the *intima* was superficially necrosed and inflamed. Pneumococci in masses were present in the thrombotic material immediately adjacent to the diseased intima, but were nowhere present in the vessel wall, nor in its vasa vasorum.

(*e*) A section from the apparently healthy pulmonary artery at a point about 1 cm. from the vegetations, but where it lay over and against the main thrombus, presented an interesting finding in that it showed one of the most recent foci of invasion of the acute disease. The adventitia and deeper layers of the media were perfectly healthy, but the intima was the seat of extensive leukocytic infiltration, its endothelium was destroyed and at one point the internal elastic lamina was elevated (endothelial lifting) in a characteristic manner above an area of acute inflammation. The intima was covered here and for a short distance by a narrow zone of recent thrombus in which numerous pneumococci were entangled.

Conclusions. 1. This case illustrates in a remarkable manner the hitherto not fully emphasized fact that a vegetative process is commonly associated with congenital cardiac defects.

2. These vegetations, in the present case, and probably in the majority of such processes occurring in conjunction with cardiac defects, are not a simple thrombosis of mechanical orgin, with secondary infection supervening, but from their onset are inflammatory in character, the result of an invasion of the vessel wall at the seat of maximum strain.

3. The inflammatory process present in this case manifestly did not arise as a result of an embolic infection through the vasa vasorum of the arterial wall, but began by the invasion of the intima at a single point, the pulmonary end of the ductus, which was prob-

ably the seat of maximum strain from the two combined causes, the eddying blood stream within its lumen, and the rigid calcareous gland which lay in close juxtaposition without.

4. The present is, so far as we know, the only recorded case in which the ductus and pulmonary artery in the neighborhood are the sole seat of the disease, and in which the pulmonary orifice of the ductus has been demonstrated microscopically to be the oldest, and therefore the initial, seat of the lesion.

5. From observation both of these and other cases we believe that the murmur, continuous throughout the cardiac cycle, but accentuated during systole, and with its point of maximum intensity over the pulmonary area, is the most important diagnostic sign of a patent ductus in adults, and when present, may be considered pathognomonic. The increased cardiac shadow to the left, the so-called *x*-ray cap, caused by the dilated pulmonary artery, furnishes valuable confirmatory evidence of patency, but is not in itself an absolute proof of its presence.

The sincere thanks of the authors are due to Dr. L. Rhea for his advice and assistance in the study of the microscopic appearances in this case and to Dr. Atkinson for the drawing, and Dr. F. Tooke for taking the photomicrograph.

Summary of Literature. A comparative study of eleven cases, including our own, recorded of infective pulmonary endarteritis about the orifice of a patent ductus reveals the following points of interest:

Localization of Vegetations. The wall of the pulmonary artery adjacent to the opening was involved in all the cases of the series, that of the ductus itself in nine, that of the aorta in seven. In three cases the vegetations involved the wall of the aorta opposite the defect (Foulis[2] Hochhaus,[3] Rickards[4]), indicating that the current through the ductus had impinged here, and that the primary seat of disease was in the pulmonary artery. The heart valves were also the seat of an infective endocarditis in the ten cases published previously to our own, and of these in three (Foulis, Buchwald,[5] Hochhaus), the lesion was multiple; in four (Kidd,[6] Schlagenhaufer,[7] Hart's two cases[8]), the aortic valve only was involved; in two (Gauchery,[9] Rickards), the pulmonary valve only, and in one

(Murray[10]), the tricuspid only was the seat of disease. *The present case was the only one of the series in which the endocardium was free.*

Infection. In Schlagenhaufer's case influenza bacilli were present in the vegetations, in Rickards' "micrococci" and in our own the Gram-positive diplococci believed to be pneumococci. In Hochhaus' case the blood culture yielded *staphylococcus albus.*

Multiple infarcts in both systemic and venous circulation occurred in the cases of Rickards, Hochhaus, Gauchery, Schlagenhaufer, Hart, and probably in our own. The clinical diagnosis of the infective endarteritis present was correctly made by Hochhaus on the basis of this feature.

The accompanying notes show the above points in detail and also the character and localization of murmur and thrill:

No. 1. (Buchwald: Deut. med Woch., 1878.) Female, aged twenty-one years. *Ductus arteriosus*—crater-like opening, with worm-eaten edges. *Vegetations: seat*—aortic valve, mitral valve, aorta, pulmonary artery, ductus arteriosus; *character*—Polypoid granulations surrounding opening of ductus arteriosus in aorta. In pulmonary artery, conglomeration of vegetations reaching from neighborhood of opening of ductus arteriosus, to just above pulmonary valves; *infection*—not determined. *Embolism*—Forked, in lung.

No. 2. (Foulis: Edinburgh Med. Jour., 1884, p. 17.) Female, aged twenty-two years. *Clinical findings*—scarlet fever at sixteen; ill eight months with anemia, increasing weakness, dyspnea, palpitation, epistaxis, and finally anasarca and hemoptysis; heaving systolic pulsation in second left interspace; loud-blowing systolic and fainter diastolic murmurs, separated by a sharp click at second left interspace. *Ductus arteriosus*—canal one-fifth inch long; funnel-shaped toward aorta, blocked by clot at pulmonary end. *Vegetations: seat*—mitral and aortic valves, pulmonary valves, ductus arteriosus, aorta pulmonary artery; *character*—large soft vegetations on ulcerated pulmonary valves, smaller on aortic valve; bean-shaped on one mitral valve; coagulum in pulmonary artery from pulmonary valves to bifurcation, extending into ductus arteriosus and right pulmonary artery, and filling saccular aneurysm on left anterior wall of pulmonary artery; lens-shaped aneurysmal bulging of aorta opposite ductus arteriosus filled with coagulum. *Embolism*—multiple infarcts in lungs. *Remarks*—pulmonary artery dilated; marked hypertrophy and dilatation of right auricle, right ventricle, and left ventricle.

No. 3. (Murray: Trans. Path. Soc., London, 1888, xxxix, p. 67.) Female, aged thirty-six years. *Clinical findings*—Always delicate, never

cyanosed; rheumatism ten years previously; thrill over pulmonary cartilage; faint murmurs; loud grating systolic murmur over whole cardia, + at pulmonary cartilage; died with symptoms of malignant endocarditis. *Ductus arteriosus*—canal, two-third inches long, admitting quill; wall of aortic opening calcified; cone-shaped. *Vegetations: seat*—tricuspid valve, pulmonary artery; *character*—large ovoid mass $1\frac{1}{2}$ x 1 inch in diameter, on upper aspect of pulmonary artery, just before orifice of ductus arteriosus, beginning beyond pulmonary valves; vegetation also on tricuspid valve; *infection*—not determined. *Embolism*—infarcts in spleen and kidneys. *Remarks*—dilatation of pulmonary artery.

No. 4. (Rickards: Brit. Med. Jour., March 23, 1889.) Male, aged seventeen years. *Clinical findings*—Always thin and pale. Precordial pain dyspnea, and night-sweats ten weeks; systolic murmur at apex, + at pulmonary cartilage; loud vibrating double murmur at second left interspace, not transmitted over sternum nor into neck; strong thrill over second left interspace. *Ductus arteriosus*—patent. *Vegetations: seat*—pulmonary valves, aorta, pulmonary artery; *character*—soft polypoid vegetations on pulmonary valves; large mass on anterior wall of pulmonary artery; round orifice of ductus arteriosus, partly occluding lumen. Small portions carried through ductus arteriosus into aorta, impinging on opposite wall of transverse arch; *infection*—micrococci in vegetations. *Embolism*—mycotic aneurysm of branch of right pulmonary artery; infarcts of lung, spleen, and kidney. *Remarks*—left ventricle slightly hypertrophied.

No. 5. (Kidd: Trans. Path. Soc., London, 1893, xliv, 47.) Female, aged twenty-two years. *Clinical findings*—dyspnea and wasting twelve months; double murmurs at aortic and pulmonary areas, and systolic murmur at mitral area. *Ductus arteriosus*—small oval opening size of goose-quill in left branch of pulmonary artery. *Vegetations: seat*—aortic valve, pulmonary artery, aorta, ductus arteriosus; *character*—Soft fibrinous vegetations on thickened, slightly incompetent aortic valve; warty vegetations on wall of pulmonary artery, just beyond thoracic valves; *infection*—not determined. *Embolism*—aneurysm of branch of left pulmonary artery; infarcts of spleen and kidney. *Remarks*—great hypertrophy and dilatation of heart, especially of left ventricle; pulmonary tuberculosis.

No. 6. (Hochhaus: Deut. Arch. f. klin. Med., 1893, Bd. 51, p. 1.) Male, aged twenty-four years. *Clinical findings*—rheumatism and endocarditis at twelve. Precordial pain, dyspnea, and symptoms of general infection two months; systolic murmur at apex; long drawn-out humming, buzzing diastolic murmur, + over pulmonary cartilage localized anteriorly, distinct in back in left interscapular region; pulmonary second loud. *Ductus arteriosus*—short canal 6 mm. wide, aortic opening funnel-shaped. *Vegetations: seat*—pulmonary valves, mitral valve, left auricle, aorta,

ductus arteriosus, pulmonary artery; *character*—vegetations on one pulmonary valve; numerous cauliflower-like yellowish-green excrescences with narrow base on anterior wall of pulmonary artery from 1.5 cm. above valves, to opening of ductus arteriosus; fresh, flat vegetations along wall of ductus arteriosus and long vegetations projecting from aortic opening of ductus arteriosus; *infection*—staphylococcus albus in blood culture during life. *Embolism*—multiple infarcts of lung and spleen. *Remarks*—heart much hypertrophied, especially in right conus; coarctation of aorta.

No. 7. (Gauchery: Centrabl. f. Path., 1900, Bd. 11, p. 70.) Female, aged twenty-seven years. *Ductus arteriosus*—hole between aorta and pulmonary artery. *Vegetations: seat*—pulmonary valves, ductus arteriosus, pulmonary artery; *character*—endocarditic excrescences on pulmonary valves extending up in pulmonary artery to opening of ductus arteriosus, forming a fringe around this similar excrescences on wall of ductus arteriosus; *infection*—not determined. *Embolism*—multiple septic emboli. *Remarks*—pulmonary artery dilated.

No. 8. (Schlagenhaufer, 1901. Quoted by Hart.) Male, aged thirteen years. *Ductus arteriosus*—patent. *Vegetations: seat*—aortic valve, ductus arteriosus, pulmonary artery; *character*—vegetations in aorta about opening of ductus arteriosus, also on aortic valves and in pulmonary artery; *infection*—influenza bacilli.

No. 9. (Hart: Case I, 1904, Virchow's Arch., Bd. 177, p. 218.) Male, aged twenty-three years. *Clinical findings*—marked anemia with intermittent fever; murmurs suggesting aortic insufficiency. *Ductus arteriosus*—large, admitting medium-sized probe; funnel-shaped towards aorta. *Vegetations: seat*—aortic valve, aorta, ductus arteriosus, pulmonary artery; *character*—grayish-red vegetations on aortic valve; wall of funnel-shaped opening of ductus arteriosus in aorta covered with pin-head grayish efflorescences which extend into ductus arteriosus; vegetations abundant in pulmonary artery extending from about opening of ductus arteriosus both to lung and heart; *infection*—not determined. *Embolism*—multiple of kidney, spleen, stomach, intestine, and heart. *Remarks*—left ventricle slightly hypertrophied; hemorrhagic nephritis.

No. 10. (Hart: Case II, 1904, Virchow's Arch., Bd. 177, p. 218.) Female, aged twenty-four years. *Clinical findings*—marked anemia, with intermittent fever. Murmurs suggesting aortic insufficiency, also long-blowing systolic murmur replacing first sound in second left interspace. *Ductus arteriosus*—patent; funnel-shaped toward aorta. *Vegetations: seat*—aortic valve, left ventricle, aorta, ductus arteriosus, pulmonary artery; *character*—cauliflower-like vegetations on aortic valve, adjacent endocardium, sinus of Valsalva and aorta near ductus arteriosus, which is plugged by a mass of vegetations extending through to pulmonary artery; intima of pulmonary

artery covered with small vegetations to medium-sized branches; *infection*—not determined. *Embolism*—multiple of kidney, spleen, heart, and lungs.

No. 11. (Hamilton and Abbott, 1914.) Female, aged nineteen years. *Clinical findings*—pale, slender; symptoms of general infection two months; leukocytes, 17,000; pneumococci in blood-culture; cardiac dulness increased in second and third left interspace (Gerhardt's sign); faint systolic thrill over pulmonary area; harsh, rumbling continuous murmur, + in systole, diminished in diastole, not transmitted upward or to back; pulmonary second, +. *Ductus arteriosus*—large canal 75 mm. long, admitting pen-holder, lined with vegetations. *Vegetations: seat*—ductus arteriosus pulmonary artery; *character*—large pyramidal thrombotic mass in pulmonary artery beginning above pulmonary valves and extending into left branch, blocking it; attached by moderately narrow base to mass of vegetations on anterior wall of pulmonary artery surrounding orifice of ductus arteriosus and invading its lumen; initial lesion at margin of ductus arteriosus in pulmonary artery; aorta and endocardium of all valves in heart healthy; *infection*—pneumococci in thrombus and blood. *Embolism*—embolic abscesses in both lungs. *Remarks*—coarctation of aorta.

DISCUSSION

Dr. Abraham Jacobi: There is one diagnostic point the doctor forgot, which is always found, and that is a continuation of the murmur along the left margin of the sternum upward into the carotids. The cases are not infrequent. In one instance I found that murmur existed a number of years. I knew the baby when he was only a few months old; he is now a boy of twelve. The ductus has been closed these two or three years. I saw him once or twice every year and always found the same symptoms, the murmur getting less and less marked until finally it disappeared not only from the carotids, but also from the pulmonary artery. That is a symptom that is never absent.

Dr. Wilder Tileston: The *x*-ray photograph exhibited by Dr. Hamilton shows the typical bottle-shaped outline, the heart and vessels in open ductus, from which a diagnosis may be made with a considerable degree of certainty.

Dr. E. Libman: Dr. Wessler and Dr. Bass have found that the presence of a marked pulsation in the pulmonary artery, as shown by fluoroscopic studies, is of great value in the diagnosis of the open ductus.

AORTIC ANEURYSM WITH RECURRENT FEVER

By ALEXANDER McPHEDRAN, M.D.
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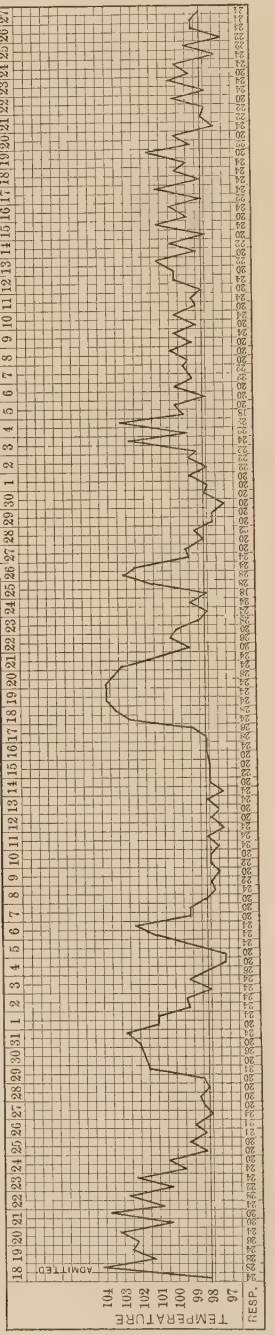
Mrs. M., aged thirty-six years, a charwoman, was admitted to the hospital October 18, 1913. She was a vigorous woman, with high color, but she said she was considerably paler than usual. Her father died of aneurysm. She had two living children and one stillbirth, twins. She lived irregularly and drank strong liquors to excess. Five or six weeks before entering the hospital she is said to have been kicked below the right scapula. She complained of pain in this part, and she was troubled with nausea and vomiting. Over the part there was dulness, and the breathing sounds were weak. There was 13,500 leukocytes per millimeter, the increase being in the polymorphonuclear cells. She did not appear seriously ill; with the fall of temperature the leukocytes returned to normal and remained so even in the recurrent attacks of fever. The signs in the chest grew gradually less marked and the pain ceased.

In the general examination of the chest signs of dilated aorta were found. Its pulsation could be easily felt below the episternal notch. Later, by the screen, a pulsating knob on the lower surface of the transverse part of the arch was seen. The Wassermann test gave a marked reaction.

She was kept five weeks under observation in order to note the natural course of the fever—it showed little if any improvement. Then mercurial inunctions were made and potassium iodide given. There was only one sharp rise of temperature after that, but slight, somewhat irregular fever persisted, and six weeks later salvarsan was resorted to. A first intravenous injection of 0.3 gm. was given. There was no reaction. Eight days later 0.6 gm. was given, still without reaction. A similar dose was given eight days later, followed by a slight short reaction, the temperature rising to 100° F., but fell to normal and remained so. A fourth dose was given after ten days, and the reaction was rather sharp, the temperature reaching 102.5° F., but again fell and remained normal. Thirteen days later the last injection was given; the reaction was less; temperature, 101.5° F. After that the temperature remained normal while in the hospital—six weeks—and her general health improved very much, but there was no change apparent in the state of the aorta or the aneurysm, and the Wassermann reaction was quite as marked.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A month later she returned for examination. She had gained much weight and strength, her color was florid, and she appeared very vigorous. She had married in the meantime.

Discussion. The object of this brief paper is to put on record a detailed statement of one of these rather rare cases of aortic aneurysm accompanied by recurrent fever, doubtless due to syphilis. That the toxemia causing the fever arises from the diseased aorta is most probable, but not certain, as it may originate in foci of disease in other parts. Dilatation and aneurysm of the aorta are due to weakening of the wall caused by the organic changes where the disease is most advanced. At first these "dilatations" will exist during life only, while the aortic wall is under tension, and may not be evident at the autopsy. It is not until they become quite large that such "pouchings" become demonstrable even with the screen or skiagram. Nevertheless they may cause serious pressure results, for example, by occluding a coronary artery with rapidly fatal results, as occurred in a case reported by Winternitz.[1]

As is usual, once the infection invades the deeper structures, such as the brain and walls of the bloodvessels, it is difficult to eradicate. Even great improvement may follow the use of any of the antisyphilitic remedies, but it is seldom that cure is effected, as shown by the persistence of the Wassermann reaction. Benefit follows even good care and generous diet; greater benefit results from the addition of mercurials, and still greater benefit follows the administration of salvarsan.

This untoward result is probably due to the slight access of the blood-serum to the spirochete, owing to the avascular granulation tissue in which it becomes embedded. Whether resort to repeated courses of salvarsan for a long period may not finally effect a cure by destroying all the spirochetes remains to be proved. There is, however, sufficient evidence to render such a course at least encouraging. The chief difficulty is in getting the patients to submit to the necessarily protracted course of treatment, especially if, as in this woman, they early become restored to a satisfactory feeling of well-being.

[1] Johns Hopkins Hosp. Bull., xxiv, No. 269, 212.

SYPHILITIC NEPHRITIS

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In recent years there has been accumulating evidence supporting the view that many cases of nephritis, chronic as well as acute, are caused by the microörganism or the toxemia of the infectious diseases. Thus scarlet fever, diphtheria, tonsillitis, la grippe, pneumonia, and streptococcic infections are reckoned among the causes of nephritis. The lesions of the kidneys differ more or less not only in the different infections but also in cases due to the same infection. There is no distinctive morphological picture by which the antecedent infection in any given case can be identified. The recognition of the etiological relationship is, therefore, based upon the sequence of kidney disease following a well-marked infection. Manifestly such a relationship is more readily established in the case of such acute infections as those named than in a chronic one like syphilis. Moreover, as syphilis in certain locations and in certain of its forms presents a characteristic histological picture, it has been difficult to accept as syphilitic processes certain conditions in which these features were wanting. Thus in the past what is now clearly recognized as syphilitic aortitis was not differentiated from other kinds of arterial disease, and in some diseases of the central nervous system a long controversy was waged over the question of their syphilitic or non-syphilitic nature. Perhaps the same denial of syphilitic etiology where the expected morphological features of a syphilitic process are wanting may account

for the relatively slight role accorded to syphilis in pulmonary pathology, and we venture to suggest that the thought may also be applicable to diseases of the kidneys. Unmistakable syphilitic lesions, such as gummata, are rare in the kidneys, but there are many cases of nephritis of various types in which the etiology is obscure, and in some of these it is not improbable that syphilis is the hidden etiological factor. Besides the instances cited (aortitis, central nervous lesions), in which the ordinary syphilitic features are wanting, we may recall the affections of various mucous membranes and hepatic, splenic, and perhaps pancreatic lesions as further instances of the same sort. It would, therefore, appear quite possible that renal disease might similarly be due to syphilis, though presenting only the features of nephritis as occasioned by other infections.

In the absence of histological evidence, and in view of the difficulty of tracing a nephritis back to such a chronic infection, the proof of the syphilitic nature of certain cases must be indirect. Perhaps in the future, investigations to demonstrate spirochetes in the renal tissue may yield results. Thus far there have been no discoveries in this direction. A few reports have been made of supposed spirochetes in the urine of cases of suspected renal syphilis, but the reliability of these reports may be questioned. Failing such direct proof of syphilis, we must rely upon statistical studies, exclusion of other probable causes, and similar evidence.

A subacute, rapidly developing nephritis has been observed in several individuals with early secondary syphilis where the kidneys had been previously healthy and where as yet no mercury had been given. Karvonen and Erich Hoffman each report a case of this type, and in both cases when, soon after the appearance of the nephritis, mercurial treatment was begun and pushed the evidence of nephritis diminished along with the other manifestations of the syphilis, and, in the course of two or three weeks, the mercury still being used, wholly disappeared. Karvonen[1] from the literature collected 9 cases in which, although the first urinalyses were made only after mercury had been given, yet there was exhibited a rapid diminution or even disappearance of nephritic manifestations under mercury therapy.

In a large number of cases nephritis has been observed in syphilitics under mercurial treatment, but this nephritis has been variously interpreted by different observers: by some as a mercurial nephritis; by others as a consequence of the syphilis.

The existence of a syphilitic nephritis was doubted by Hunter and Wells, and Blackall (1818) attributed the edema and albuminuria complicating some cases of syphilis not to the disease but to mercury. In 1840 Rayer strongly opposed this view and described 3 cases which he considered syphilitic nephritis. Subsequent to these reports many instances of supposed syphilitic nephritis were recorded, and while critically examined, as has been done by Karvonen, more than half fail to be convincing, there yet remains a considerable group of scarcely disputable cases.

Nephritis may be recognized in the secondary stage of syphilis occurring as an acute nephritis remarkably early in the disease, usually in the first two or three months. Fournier describes this form as characterized by an insidious onset, by a great quantity of albumin in the urine, by the rapid development of the condition, and in the severer cases by an early development of uremia; the urine is diminished or there may be anuria. In many respects the condition resembles a postscarlatinal nephritis. Fournier has described such kidneys pathologically as among the large white kidneys with marked tubular degeneration, but frequently also with extensive endothelial hyperplasia and interstitial change, in which respect again they resemble scarlatinal nephritis. In Fournier's experience about one-third of these patients succumb; however, Karvonen found a large proportion of recoveries, while Rose Bradford has noted a tendency to a remittent course with persistence especially of the albuminuria.

In the later stages of syphilis, amyloid kidney and interstitial nephritis are the most frequent forms of renal disease, but other types of nephritis have been observed. In 186 autopsies on individuals with acquired syphilis, Spier (1877) found 125 with renal lesions, of which 36 were amyloid kidneys. Gummata of the kidney are rare; in Spier's series of autopsies on syphilitics they occurred in 4 per cent., and in Fournier's series in less than 1 per cent. Karvonen described 2 cases of renal gummata and collected 28 cases

from the literature. There have been a number of reports of nephritis developing in late syphilis which were apparently cured by antisyphilitic treatment and a large number in which improvement occurred.

In congenital syphilis the renal lesions are more often those of defective development than of nephritis, and rarely give rise to symptoms of urinary change during life. Of late hereditary syphilis the commonest renal manifestation is amyloid disease, and the onset of symptoms is usually insidious, the first being often edema. In addition to amyloid there may develop interstitial or parenchymatous nephritis or rarely gummata.

The latest addition to our conception of syphilitic nephritis has been suggested by Munk.[2] He noted the occasional presence of doubly refractile lipoids in the urine of individuals with severe nephritis of any etiology, but found them so abundant in those cases in which he had grounds for suspecting a syphilitic etiology as to warrant, he believed, the recognition of a peculiar relation between syphilitic nephritis and the presence of doubly refractile lipoids in the urine. Munk attempted to describe the clinical features of the cases of nephritis of syphilitic origin, and noted particularly the decided albuminuria and abundance of casts of various types as well as a pronounced and persistent edema. These doubly refractile lipoids under the common microscope resemble neutral fat globules, but when examined with polarized light show a dark central cross separating four bright peripheral quadrants. This optical peculiarity was first observed in 1858 by Mettenheimer in the lipoids in certain alcoholic extracts. Müller and Schmidt noted much later doubly refractile globules in certain sputums. The chief impetus, however, to the study of these substances was given by Kaiserling's discovery in 1895, that the fatty globules of the adrenal cortex are doubly refractile. Since that time extensive studies of these bodies have been made by Kaiserling and Orgler, Albrecht, Dietrich, Panzer, Lehmann, Adami and Aschoff, Windaus, Smith, Ciaccio, Fischler, Kawamura, and others, which have led to a considerable knowledge of their chemical and physical nature, their staining reactions, and their normal and pathological distribution. The lipoids, which are known to give rise to doubly

refractile globules, include cholesterin esters, mixtures of cholesterin and fatty acids, sphingomyelin, cerebrosides, and certain oleic acid soaps. The physical condition of these doubly refractile globules is one for which Lehmann proposed the name fluid crystals, and appears to be an intermediate state between true fluids and true crystals. Changes in physical conditions, such as drying, heating, freezing, or the action of solvents, cause the disappearance of the peculiar optical properties of these substances; but subsequent manipulation may restore the fluid crystal form and with it the optical properties. Chiefly through a study of the reaction of the various doubly refractile lipoid substances to staining methods it has become possible, in some degree, to distinguish microchemically between the types, and from the studies of Aschoff and his coworkers and of Kawamura,[3] confirmed by the chemical studies of Windaus,[4] it seems probable that the doubly refractile lipoid globules occurring normally and pathologically in man and mammals are cholesterin esters. Normally these globules have been seen in the adrenal cortex, the thymus, the lutein cells, the puerperal uterus, the mesentery, and the choroid plexus. Pathologically they have been observed in atheromatous areas of the arteries, in amyloid kidney, in chronic nephritis with marked cellular degeneration, in the urine of nephritis, in albuminuric retinitis, in the epithelium of the pulmonary alveoli in pneumonias or tuberculosis and in the neighboring lymphatics and sputum, in the gall-bladder epithelium and that of the hepatic ducts during cholangitis, in pyogenic membranes, in chronic mastitis, mesenteric tabes, actinomycosis, xanthomas, and in certain neoplasms (especially carcinoma, sarcoma and hypernephroma). The process by which these lipoid globules appear in degenerating cells, whether by infiltration or by decomposition of more complicated lipoid-containing substances already present in the cell, remains unsettled, but their appearance pathologically in a cell is considered evidence of a severe cellular degeneration which is not reversible and of much more serious significance than the common glycerin ester type of fatty degeneration.

With these facts before us we felt that a further study of the clinical significance of the appearance of these doubly refractile lipoids in the urine, and especially of their possible relation to a

syphilitic nephritis, was desirable. For this purpose we have examined the urine with a polarizing microscope fifty-eight times from 46 cases. Of these 46 cases, 23 showed nephritis with an abundance of albumin and casts in the urine. Of these 23 cases, 6 had positive Wassermann, 3 had strong presumptive evidence of syphilis but not positive Wassermann, 14 had not the slightest evidence of syphilis. The 6 cases with positive Wassermann all showed lipoids in the urine, whereas of the 14 non-syphilitic cases only 5 showed lipoids in the urine. The rest of the 46 cases studied were made up in part of nephritic cases of the interstitial or arteriosclerotic types, with only traces of albumin in the urine and a few hyaline and granular casts, some with syphilis and some without; in part of syphilitic cases with no nephritis and in part of control cases with neither syphilis nor nephritis. None of these cases showed lipoids in the urine. It is of interest that one of the 6 syphilitic cases with nephritis showing lipoids in the urine, had not received any mercury. (The accompanying table presents the figures more clearly.) There is, we believe, evidence in these figures to suggest that there exists a parenchymatous type of nephritis due to syphilis, characterized by an abundant albuminuria, with many hyaline, granular, and occasionally epithelial casts, with a tendency to produce edema of renal distribution, associated, as a rule, with a moderate reduction of phthalein output and exhibiting an almost constant tendency to the presence of doubly refractile lipoid globules varying in size from that of an erythrocyte to globules three or four times this diameter, seen sometimes floating free in the urine but not rarely as a constituent of a compound granular cell or possibly upon an epithelial cast. On the other hand, similar lipoid globules may be found in severe acute or chronic parenchymatous nephritis of other etiology, but in only a minority of cases. It may be added, however, that with but one exception in our series the cases which showed abundance of these lipoids in the urine were syphilitic.

LIPOIDS IN URINE

	Total.	Lipoids in urine.
Nephritis with severe albuminuria:		
Nephritis with syphilis	6	6
Nephritis, syphilis doubtful	3	2
Nephritis without syphilis	14	5
Interstitial or arteriosclerotic nephritis (albumin in traces only), some syphilitic, some non-syphilitic	23	0

In order to determine whether the common experimental degenerative nephritis of animals would be associated with lipoids in the urine, three rabbits were given a uranium nephritis, and one dog a chromate nephritis. The four experiments were negative; no lipoids were found in the urine. Further experiments with mercurial nephritis, phosphorus, and chloroform lesions and syphilitic inoculations are in progress.

We found of further interest the fact that of our last 84 cases of nephritis, for 66 cases there could be recognized from the histories, such possible etiological influence as infections, lead, alcohol, excessive work, exposure, senility, etc.; but that for 18 cases no such factors could be determined. Of these 18 cases, there existed in 8 either an unquestionable history of syphilis or a positive Wassermann or both; in 6 more of these cases no Wassermann had been secured; while in 4 syphilis was definitely excluded. It is perhaps significant that syphilis should have been present in so many of the otherwise unexplained cases of nephritis.

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DISCUSSION

Dr. Abraham Jacobi: I would like to say a good word for mercury. Chronic nephritis in all sorts of conditions has been my despair as, I suppose, it has been the despair of every general practitioner. Most of them die as we all know. Some decades ago it was attempted to use mercury in cases of chronic nephritis of the interstitial variety, and I may say that I believe a great many cases have done fairly well under mercurial treatment, even where I was quite sure there was no syphilis in the case. I believe we have been too much in the habit of relying on mercury as an antisyphilitic treatment. It is a mistake, and in such cases that are our despair, I have encouraged those who have had to deal with these cases in general practice to rely now and then on mercury. I believe it is worth while.

Dr. James Tyson: After dabbling in this subject for nearly fifty years, I must confess that the syphilitic kidney continues to be to me an enigma, and I do not think Dr. Stengel has altogether cleared it up. There seems to be no way of making a diagnosis of syphilitic kidney except inferentially unless some additional aid is given us. The Wassermann tells us simply that there is syphilis, not its site. Again shall we conclude that every case of chronic nephritis occurring in a person with syphilis is syphilitic? We have the same symptoms in people not syphilitic. If, for the sake of justifying treatment we conclude every case of chronic nephritis associated with syphilis is syphilitic shall we treat it with mercury? We have been taught, and my observation seems to confirm this conclusion, that mercury in large doses is rather harmful than beneficial in any form of nephritis. Shall we take the risk and make a trial of it or trust to the older methods of treatment, with a sense of security in the fact that we cannot do any harm if we are not doing any good? Have the modern tests and treatment of syphilitic conditions helped us any in syphilitic nephritis? I have had little opportunity to judge of them, but lately a case has come under my observation like this: Nine months ago a young man contracted what was said to be syphilis. Examination microscopically of the ulcer confirmed the diagnosis by finding the spirochete in the local lesion and the Wassermann test further confirmed the diagnosis. No other symptoms appeared. Some months further subsequent to the exposure, no other sign had presented itself, but some months later still (March 15, 1914), he slept two nights in a chamber freshly painted with turpentine paint. Succeeding this exposure a slight edema of the face suggested an examination of the urine and it was found to contain large quantities of albumin with casts. It will be remembered that some months after exposure to syphilis the urine was free, but between that date and the exposure to turpentine there was no examination. A recent Wassermann test since the exposure to turpentine was positive. Now, under the circumstances, shall salvarsan be tried in the way of treatment? I have had no experience with it. I only have a wholesome dread of mercury while in one case reported to me the result was harmful rather than beneficial. I am pleased to learn of the favorable results reported by Dr. Stengel.

Dr. F. C. Shattuck: In corroboration of Dr. Tyson's remarks, I should like to say that for many years it has been my practice, and also my teaching, to exercise care in giving mercury in any case of nephritis of non-luetic origin. In uncompensated heart cases, the presence of albumin and casts has not deterred me from the use of calomel, either as a purgative, or in doses of three grains every four hours for several days as a diuretic, provided that passive congestion could be credited with the kidney disturbance. Mercury, like lead and arsenic, is an irritant to the

kidneys, and I have seen nephritics salivated by a single dose of calomel. The list of purgatives is long and varied, and it seems to me safer, when the kidneys are damaged, to use non-mercurial agents, as a rule.

Dr. Solomon Solis Cohen: The remarks of Dr. Tyson prompt me to cite two comparatively recent cases in which, in spite of the apparent counter-indication of albumin and casts in the urine, salvarsan was used with happy result. In neither case was there a clear syphilitic history. The first presented symptoms that had been termed "angina pectoris," but which I rather believed to indicate syphilitic aortitis, basing this opinion upon my previous observation of like conditions. The other case has been called "asthma;" but the symptoms appeared to me to be dependent upon combined cardiac and renal lesions. Ocular findings roused the suspicion of syphilis. The Wassermann reaction was positive in both instances. In these cases salvarsan was used cautiously and the patients were kept under close observation for two weeks following the intravenous injection. So far from increasing renal irritation, the albumin diminished, the casts disappeared, and the symptoms referable to the underlying lesions have also disappeared. Of course, mercurial and iodide courses were given, following salvarsan.

ACONITE AS A VASODILATOR

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One of the important questions in modern therapeutics is how to regulate arterial blood-pressure, particularly when it rises above normal. Morbid conditions due to high pressure are very numerous and equally varied in their causation. We should, therefore, readily recognize it when present, and be fully aware of its special dangers in each case. This paper proposes to discuss only the medicinal agents which may be used to lower blood-pressure, and how they may be administered.

The commonest drugs employed heretofore for this purpose are the various preparations of the nitrites, such as amyl nitrite, nitroglycerine, potassium nitrite, and erythrol tetranitrate, named in the order of the duration of their action. The type of them all is amyl nitrite, whose action is so rapid that it is used only in sudden emergencies, as in attacks of angina pectoris. But the chief objection to amyl nitrite is that its action is not only sudden, but very evanescent, which applies also to all nitrites when the conditions of disease for which vasodilators are indicated is taken into account. These morbid conditions are usually chronic in both their origin and cause, such as the processes ending in arteriosclerosis, chronic interstitial nephritis, or in sclerosis of nervous tracts.

These slowly induced textural changes are ordinarily caused by arterial ischemia, and either for their prophylaxis or for their management, all nitrites are of little service, owing to their temporary action. Meantime the organic changes in the walls of the arterioles lead to the obliteration of wide areas of both the arterioles and the capillaries of the affected parts. This alteration is well illustrated in chronic interstitial nephritis, when on baring the

unnaturally white skin of the abdomen, it will be found comparatively difficult to produce a reddened mark by drawing the finger nail across it. In phthisis, on the other hand, the same procedure easily causes a scarlet line to follow the finger nail. But that which causes the cutaneous anemia must likewise occur in the capillary circulation of the internal viscera, and thus interfere with their functions. Now as the chief business of the kidneys is to eliminate urea, I have found that in chronic interstitial nephritis there is a characteristic and marked decrease in urea elimination.

My objection to all nitrites, as above stated, is that their vasodilating effects are too transient, the most prolonged of them, that of the erythrol tetranitrite, lasting for less than an hour, which is by no means sufficient for such a permanent morbid condition of general arterial contraction, with heightened blood-pressure, as is present in chronic interstitial nephritis.

After an experience of years in its use for this purpose, I regard aconite as the most efficacious vasodilator which we possess, when given systematically in full doses. Aconite thus administered at once reduces blood-pressure, produces a full and compressible pulse, and greatly increases the percentage of the elimination of urea in interstitial nephritis.

We may here briefly allude to some contrasts between the clinical features of parenchymatous and interstitial nephritis. In parenchymatous nephritis the kidneys are large and white in color, while in interstitial nephritis they are shrunken and red. In parenchymatous nephritis, albumin is abundant in the urine, in interstitial nephritis it is either wholly absent or present only in slight amount. In parenchymatous nephritis there is anasarca from beginning to end. In interstitial nephritis every sign of dropsy may be absent. In parenchymatous nephritis the urea elimination may be but slightly below normal, while in interstitial nephritis the urea is diminished from the start, below that of any other form of kidney disease.

The most important action of aconite when administered in interstitial nephritis is to increase the elimination of urea. In a former paper read before this association I stated that in a series of cases which I had observed in my wards in the Roosevelt Hospital,

the elimination of urea after the administration of aconite, was increased, in a large proportion of these patients to double the amount, previous to the administration of aconite, and in two cases, to three times the amount. In a series of 7 cases of chronic interstitial nephritis observed for two weeks by Prof. J. Edgar Welch, Dean of the Department of Medicine, at Fordham University, the property of aconite to increase the output of urea was not observable until Dr. Welch himself raised the strength of the aconite from that of the present pharmacopœia, which is only 10 per cent., to the pharmacopœia of 1890, which is 33 per cent., and which was the strength of the preparation which I used in my above observations at the Roosevelt Hospital. On doing so, Dr. Welch found that the elimination of urea was immediately increased to the extent that I had observed. I have given as much as 10 drops of this strongest tincture 4 times a day with excellent results in the reduction of pressure.

The symptoms produced by heightened blood-pressure are usually distinct shortness of breath, often with a sense of oppression at the epigastrium, very perceptibly increased by muscular exertion, such as by walking or by ascending stairs, and especially by walking against the wind. Patients in such a condition are frequently obliged to stop, as they express it, "To catch their breath." Not uncommonly actual anginose pains come on, with attacks of dizziness. In one case, a lady now seventy-four years of age, these symptoms were formerly very troublesome, but by perseveringly taking the aconite three or four times a day, she has been free altogether from them for twelve years, provided she does not omit the aconite.

Another case was that of a well-known physician, aged sixty years, a somewhat fleshy man, with a large chest, and a blood-pressure of 185 mm., who had severe attacks of anginose pains, waking him about 2.00 A.M., which passed down the left arm to the wrist. He was treated with the 10 per cent. tincture of aconite, 15 drops, combined with 5 grains of sodium iodide, t.i.d., whereupon all his symptoms improved, and his blood-pressure dropped from 185 to 160 mm. After continuing this line of treatment for two years, he reduced the aconite to only 10 drops, with an entire disappearance of his old symptoms.

The beneficial effects of aconite are particularly pronounced in mental derangements of the nature of melancholia with high blood-pressure. Thus a patient of mine had been gradually passing from a state of melancholia with hallucinations about being financially ruined, until he became maniacally insane, and repeatedly tried to break through the windows. He was then treated by Dr. J. Edgar Welch who had to employ three men to hold him while he was taking his blood-pressure. Dr. Welch by my directions gave him 15 drops of the 10 per cent. tincture of aconite and 15 drops of the tincture of veratrum veride every half hour. He took six of these doses before he became quiet, after which he remained permanently better, and in a few weeks was able to resume business, meantime taking 15 drops of the 10 per cent. tincture of aconite, four times a day, to prevent a relapse.

As a veteran teacher of Materia Medica, I insisted upon the fundamental difference between functional and organic or constitutional medicines. Functional medicines like aconite or opium produce their whole effects in one dose, and however often repeated, the effect of the last dose is no different from that of the first. Organic or constitutional medicines, on the other hand, like iron in chlorosis, and mercury in syphilis, do not produce their effects except by the cumulative action of many doses. Therefore the proper dose of a functional medicine is not reached till it causes its own symptoms. In the above case of maniacal melancholia I was obliged to give 180 drops in the course of three hours, because any less quantity would have produced no effect.

A few years ago I was asked by a gentleman to prescribe for his widowed sister, Mrs. G., without seeing her, because in her then condition she refused to see any physician, or to take any medicine. His story was that she had been subject to severe melancholia until she became maniacal, and had to be committed to an asylum, in which she remained for about six months. She was then allowed to go home where she remained for nearly two years, attended by a trained nurse, but as above mentioned, in strict seclusion. Her high blood-pressure, and this gentleman's description led me to conclude that she was affected by melancholia, and without seeing her, I prescribed aconite, given by her nurse before each meal without

the patient's knowledge. She at once began to improve in her mental state. Noticing, however, that she became nervous and excitable toward night, I concluded to add a fourth dose of the tincture of aconite in the evening. After this she wholly recovered, and began to gain flesh, remaining in excellent health and spirits until her death, which occurred in her sleep, as hereinafter detailed by her brother in a letter to me.

"My sister passed away in her sleep Saturday morning, May 3. She owed to you five years of health and happiness, and I owe you a debt of gratitude which no words can describe. It seems to me in the interest of humanity, your treatment by aconite should be known in the various institutions where circulatory troubles are diagnosed as diseases of the brain."

DISCUSSION

Dr. James Tyson: My experience with tincture of aconite has been such that I should be afraid to use such large doses. I have known five minims to produce a mild toxic effect.

Dr. Abraham Jacobi: I learned to use tincture of aconite in cases of sclerosis through the author of this paper many years ago, and I have used it a great deal since then. I am reminded of the warning given by Dr. Tyson, for I have given as many as 30 drops, 3 or 4 times a day, in such cases where I thought it was indicated. I have in cases of chronic arteriosclerosis given it in 10, 15 and 20 drops, 4 times a day, and have given it for a long time.

Dr. Thomson: In the first place, I never in my life gave 16 minims of aconite to anyone. That would mean 30 drops of fluid, but I have found that in these conditions there is a great tolerance for aconite, particularly in cases of interstitial nephritis. They are able to take large doses, whereas healthy persons could not do so without deleterious effects.

EFFECTS OF HEREDITY IN BOVINE TUBERCULOSIS

By HARLOW BROOKS, M.D.
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That a very high percentage of dairy cattle are tuberculous, that is, are "reactors" is a universally admitted fact. State and municipal laws are more and more insisting that the milk of tuberculous animals shall not be sold, and the question of bovine tuberculosis has now become a serious economic as well as hygienic problem. When one realizes that for general use milk must be furnished at a rate which can be paid by the average citizen and at the same time appreciates the fact that the dairyman must expect from 15 to 50 per cent. of his stock to be ruled out if the tuberculin tests are rigidly enforced, the problem of milk supply becomes a factor of very great difficulty as well as importance. A further fact of great bearing is the strong probability that the more highly blooded cattle are most likely to be found to be reactors. This makes the problem of the honest and ambitious dairyman even more difficult, for if he attempt to increase the quality of milk or butter production of his herd, he almost invariably breeds in tuberculous stock, and unless extraordinary and expensive methods of isolation are practiced dissemination of the infection is almost certain to follow. On the other hand, if he fails to thus improve his stock he is very likely to get into trouble because the quality of his milk may be found deficient and he thus also lays himself liable to prosecution.

The difficulty of improving breed is a very serious matter, particularly for the farmer of small capital since the price of blooded stock is always high and he is very likely to purchase as non-reactors cattle which have been "plugged" against the tuberculin reaction by dishonest dealers. This trick of "plugging," though familiar to most stock men, I find is not widely known by physicians and there is no doubt but that when tuberculin tests are known to be about to be

made, this method is practiced so that negative tuberculin results are obtained even in cattle which may be extensively so diseased. "Plugging" is performed by injecting a dose of tuberculin a few days before the public or legal test. For some time after the reaction which follows this injection, subsequent tuberculin tests are negative, so that even widely diseased animals may be tested and sold apparently as free from tuberculosis. As can be seen, detection of this fraud may be practically impossible.

Another point often unrecognized by the hygienist is that the tuberculin test in cattle as in man is positive in animals which while they may harbor foci of the disease are not actively tuberculous, that is, the reaction may be given by cured cases. If we were to apply to man routine tuberculin tests it is certain that we should find many supposed and actually healthy individuals who would respond to the reaction. The term "Reactor" is therefore indiscriminatively applied by stock men to animals perhaps not actively or obviously tuberculous and yet which simply give the reaction. It is found, however, that when such stock, apparently otherwise sound, be housed and fed with perfectly healthy non-reactors the non-infected herd sooner or later become widely diseased for the sensitiveness of uninfected animals to tuberculosis is remarkable and apparently much greater than in man. The common practice of dairy men is to largely ignore this fact, to take the chance as part of the risks of the business, and to eliminate only such animals as are obviously sick. These usually form but a small percentage of the real reactor group and under such methods the disease can never be eliminated from any herd.

The problem then becomes very complex particularly from an economic standpoint. It is true that thorough pasteurization of milk will eliminate the possibility of transmitting tuberculous infection to man. I do not propose to enter into the discussion of this problem at this time but to especially point out that reactors in any herd eventually cause the more or less complete infection of that group.

The experiments conducted at Woodcrest, previously reported,[1]

[1] Trans. Soc. Exp. Med. and Biol., 1914, xi, 50.

have apparently furnished a solution for this problem though it must be admitted a very expensive one indeed for the breeder of moderate capital since it practically necessitates separate and distinct establishments and personnel, and enough capital to permit a more or less idle and non-productive group of animals.

To me personally the fact of greatest interest has been that the inbreeding of tuberculous animals has in no way impaired the type or desirability of the offspring. It has been conclusively shown that the offspring are very rarely, if ever, infected before or at birth. That the slightest carelessness in exposure of the newborn calves to infection leads to certain disaster is illustrated by ten recent infections at Woodcrest through the negligence of one workman in not minutely following out the instructions laid down. Tuberculous animals of desirable types may therefore be freely used for breeding purposes provided that the calves are not allowed to come in contact with the infected parents. The economic as well as the biological importance of this apparent fact is obvious.

To establish the fact that reactors may furnish and perpetuate most desirable traits as to type, fertility, milk and cream production, and to therefore controvert the suggestion that such infected animals should be utterly destroyed, notes of the following group of animals are presented, taken by permission of Mr. Dimick from the records of Woodcrest Farm.

Pietje 22d, No. 70884. The foundation dam of this strain was imported from Holland by the Woodcrest Farm. She was supposedly of the highest type representing the Holstein-Fresian breed and her pedigree shows descent from the finest animals of this stock. It has not been possible to ascertain whether or not she was derived from tuberculous parentage but early tests at the Woodcrest Farm showed her to be a "reactor" although apparently in perfect health. She died of generalized tuberculosis at the age of fourteen years, four months. She is credited with four calves born in Holland and seven in this country. She made the following remarkable record:

Butter, seven day test	31.62 pounds
Milk, seven day test	673.90 "
Butter, thirty days test	128.37 "
Milk, thirty days test	2786.40 "
Butter, six months test	566.60 "

This last item is stated to be the world's record for butter production for this time. During this same period she produced 13,673.90 pounds of milk. While at the Woodcrest Farm she gave birth to an annual calf with records as follows:

(1) Woodcrest Pietje. A bull calf; a perfect and effectively fertile specimen, sold as a herd bull. This animal is not known to be tuberculous, although it is strongly probable that he is.

(2) Pietje 22d's Woodcrest Lad. This animal is a perfect specimen in every respect and has been retained at the head of the Boutekou Farm as a stud animal. He is known to be tuberculous and is isolated with the tuberculous herd. A daughter of this animal has produced at the age of four years 35 pounds of butter in seven days. This is stated to be a world's record for this age.

(3) Pietje 22d's daughter. This animal at birth was a perfect specimen in every apparent respect, although she was found to be tuberculous in the second year of her age. Her record is as follows:

Butter, seven days	25.19 pounds
Milk, seven days	553.40 "
Butter, thirty days	104.29 "
Milk, thirty days	2202.22 "

She was fertile each year and her offspring have all been perfect specimens of their kind. She died in January last from a generalized tuberculosis one week after the delivery of her last and perfect calf. This animal has not yet been submitted to the tuberculin test but inasmuch as it was removed from the mother immediately after birth, from previous experience, it is assumed to be non-tuberculous. She was the dam of Woodcrest Jamaica Pietje; a bull calf, perfect in every respect and now the head of a valuable herd. This animal has proved to be normally fertile. A daughter in her second year has given a butter record for seven days of 16.07 pounds, and of milk for the same time of 350.30 pounds. Woodcrest Jamaica Pietje was removed from the dam at birth, isolated from the tuberculous herd, and is free from any disease. Also dam of Woodcrest Johanna Pietje: A perfect and fertile bull. He is free from tuberculosis as he was removed from the dam immediately after birth. Dam also of Woodcrest Pietje Pontiac: A perfect male specimen removed from the dam immediately after birth and consequently

free from disease. This animal was sold while a calf for $2000, and is the anticipated head of a valuable herd.

(4) Pietje 22d's second daughter. This animal has always been tuberculous having received the infection apparently from her dam shortly after birth, nonetheless she was in every way a perfect specimen and gave a record of butter production for seven days of 29.63 pounds; of milk in the same period, 584.70 pounds. Butter thirty days, 117.24 pounds; butter for one year, 829.53 pounds. Milk for the same time, 19,722.90 pounds. This animal died apparently from a generalized tuberculosis in September, 1913. She had been fertile each year since her maturity and all her calves were normal specimens. Three of these offspring are recorded all perfect, typical, and fertile in every way.

(5) Pietje 22d's son. This animal is a perfect specimen, although found to be tuberculous at the age of one year. He is at the head of a herd, serving about 100 animals yearly; is very fertile and typical of the breed in every way. His first five daughters at two years of age average over 18 pounds of butter in seven days each and over 4 per cent. of fat.

(6) Pietje 22d's third daughter. Found to be tuberculous at three years of age; after having successfully passed two prior tests. Her record shows butter production in seven days, 16.07 pounds; milk production seven days, 302.30 pounds. This animal is the dam of one heifer which has not yet freshened but which is a perfect specimen of her class.

(7) A bull calf, the last offspring of this remarkable cow, died of an infantile diarrhea in its very early youth, before it had been registered.

The male parentage in many if not most of these instances has been also tuberculous in all probability. The question of whether or not the offspring became tuberculous depends entirely upon exposure after birth. The point of greatest importance illustrated by this remarkable family is that no defects of a biological nature have been found in any of the offspring of this definitely tuberculous stem. All are perfect specimens. There has been no reduction in fertility and judging from the milk and butter records no diminution

in butter or milk production, and as stated, several world's records have been attained by these animals.

This family is apparently fairly illustrative of others of like class, and in so far as the observations go it seems definitely demonstrated that parental tuberculosis in the cow causes no defects to be apparent in the offspring even though the calf be born in the almost terminal stages of the disease in the dam.

This report is intended to point out that the term "reactor" as used by stock men often means what in human medicine would be classed as healed tuberculosis. It seems to show that definitely tuberculous animals may be safely utilized for breeding purposes and that they may be crossed and inbred with entire disregard of the factor of tuberculosis and purely for the purpose of improving or maintaining type. Most important of all, the fact stands out that although it may not be wise to utilize the unpasteurized milk of the reactors for human consumption nor yet for the feeding of calves or other animals, yet reactors may be successfully and safely used as brood stock and thus cease to be an economic waste.

THE INFLUENCE OF BENZOL INHALATIONS ON EXPERIMENTAL PULMONARY TUBERCULOSIS IN RABBITS

By WILLIAM CHARLES WHITE, M.D.

AND

A. MARION GAMMON

(R. B. Mellon Research Laboratory, Tuberculosis League of Pittsburgh, Pa.)

Benzol, C_6H_6, is the best solvent for the fat portion of the tubercle bacillus. It extracts a greater percentage of fat than any other single solvent will take from the bacillary substance. Because benzol can be easily vaporized and utilized as an anesthetic, it was thought possible in this way to dissolve the living tubercle bacillus after its entrance into the pulmonary capillary system by way of the ear vein and before the formation of the tubercle.

It was hoped in this way to obtain a solution of all the living portions of the tubercle bacillus within the body and the possible development of a retardation of the process produced by a fatal dose of tubercle bacilli and the establishment of an immunity to a further dose of the organism. Contrary to the desire expressed in the theory, we found that in every instance whether the infecting tubercle bacilli were of low virulence or of high virulence, the resulting infection in rabbits was very much more severe in those treated by inhalations of benzol than in those infected with the same weight of infecting organism.

Inhalations were given from a wide-mouthed glass staining bottle with absorbent cotton in the bottom of the bottle. The mouth of the bottle was held lightly over the mouth and nose of the rabbit so that very little benzol gas was wasted.

Symptoms Produced by Inhalations of Benzol. The symptoms produced in rabbits by the inhalation of benzol were similar to those described by Torald Sollmann[1] for the inhalation of gasoline vapors. There is immediately increased rapidity and depth of respiration; the animal struggles violently to escape with a forward projection of the head, and usually in from two to five minutes incoördinate convulsive movements begin; the animal becomes unconscious before the end of three minutes when it may be laid on its side on the table. Even though unconscious, the four legs during this period keep up a coördinate movement, such as the animal would have in jumping. Finally, complete relaxation, retraction of the head, with a glassy stare of the eyes which remain open and usually retain the corneal reflex. If the benzol is pushed too rapidly, the animals may have severe convulsive movements ending in death.

Many of our animals apparently died with respiratory death, but were easily brought back to life by artificial respiration carried out in the fresh air. At times three minutes elapsed between the apparent death and the beginning of recovery. The longer the time consumed in giving the benzol, the less the convulsive movement.

In beginning recovery from anesthesia, the jumping movements of the legs begin again and the animal often screams as if very frightened. As the animal begins to attempt to get on its feet, its legs sprawl and it has no control over them; it staggers as if intoxicated and can be moved with the foot without giving any evidence of muscular control over itself. Finally, it makes a jump or two and in twenty to thirty minutes seems to have recovered.

Rabbits may be given 5 c.c. of benzol every second day for at least four weeks without death ensuing. The largest amount given any one rabbit was 40 c.c. during four weeks. The inhalation of benzol did not in any way interfere with the apparent health of the rabbits as they ate well and gained in weight during the observation period. In all 33 animals were used, 12 controls and 21 treated.

Where the amount of tuberculosis was slight owing to the avirulence of the germ used, very little clinical evidence was apparent in the animals. At death, however, the spleens were large in most of these and the bone marrow showed the changes described below.

[1] Text-book of Pharmacology, Philadelphia, 1912, p. 437.

The blood changes in the animals during life are shown in the following table:

LEUKOCYTE COUNT

CONTROL RABBITS

	No. of rabbits.	Lowest count.	Highest count.	Average count.
End of first week	6	8,800	19,600	13,000
End of second week	5	10,000	21,000	13,000
End of third week	3	9,800	10,600	11,400
End of fifth week	2	9,000	12,000	10,800
End of sixth week	2	10,600	15,000	12,800
End of seventh week	2	10,600	10,800	10,700

BENZOL TREATED RABBITS

	No. of rabbits.	Lowest count.	Highest count.	Average count.
End of first week	14	6,600	15,200	11,200
End of second week	11	6,400	12,000	8,000
End of third week	13	4,000	12,400	7,000
End of fifth week	4	5,200	8,000	6,600
End of sixth week	3	5,600	7,200	6,200
End of seventh week	4	3,800	9,800	7,600

The blood was obtained from the ear vein of the rabbit suspended by its hind legs so that a free flow was obtained.

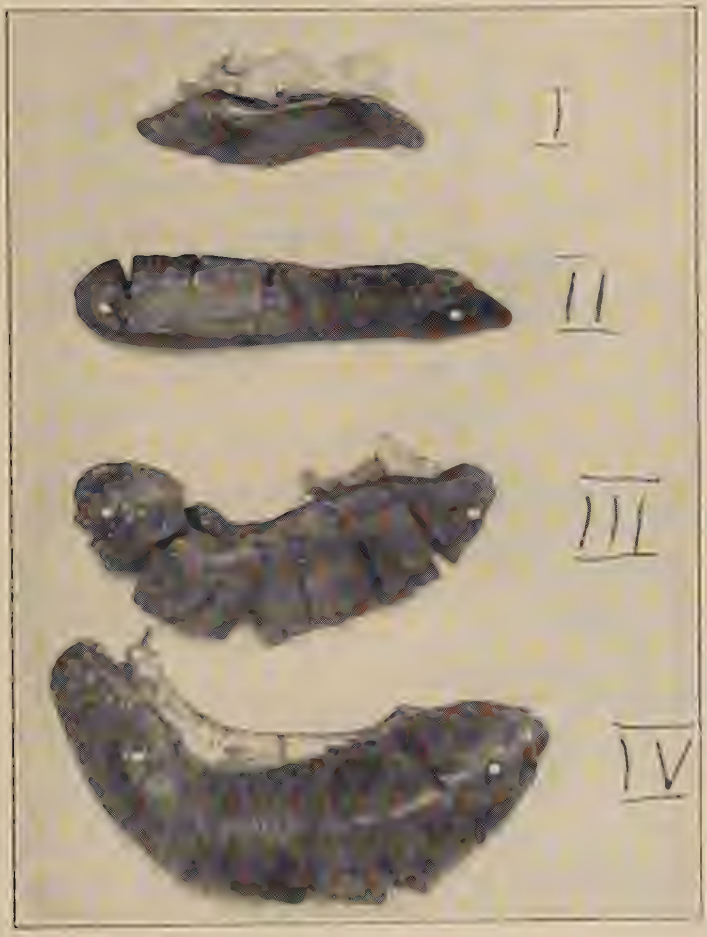
It will be seen that there is a steady decline in the white blood count of all the treated animals. The lowest count was 3800 cells per cmm. which was at the end of eight weeks, or six weeks after treatment with benzol was discontinued. The increasing persistence of the leukopenia weeks after the inhalations were stopped was the most striking feature of these counts. The diminution of cells was wholly confined to the polynuclear, acidophile, granular cells of the blood. In a hundred cells the percentage lost by the reduction of the above cells was made up by the small and large lymphocyte cells of the blood.

The number of red cells was not materially changed in the treated rabbits as a rule, although in one instance four weeks after the inhalations of benzol were stopped, there was found a red cell count of 3,318,000, with a leukocyte count of 5200 cells per cmm.

There was, in all the treated animals, a very noticeable decrease in the number of platelets by the end of the second week. This decrease persisted till the death of the animals.

Postmortem Changes. Hemorrhages. In only one of the rabbits was any purpura or hemorrhage found at autopsy. In this animal

which had received 35 c.c. of benzol in three weeks there were numerous hemorrhages into the mucous membrane of the stomach and intestine.



No. 1 is a normal spleen from rabbit 3300 grams in weight.

No. 2, tuberculous spleen (full-grown rabbit). Weight of rabbit at death, 1100 grams.

No. 3, tuberculous spleen of benzol treated rabbit—treated in similar way to No. 4.

No. 4, tuberculous spleen of benzol treated tuberculous rabbit, 35 c.c. of benzol by inhalation, treated every day for two weeks—lived after treatment was stopped four weeks. Lowest white blood corpuscles, 7800.

Size of spleen: Length, 13 cm.; circumference, 9.5 cm.; width, 3 cm.; depth, 3.5 cm. Weight of rabbit, 1442 grams.

Splenic Tumor. The most striking feature of the autopsy in most of the treated animals was the splenic tumor. In one animal, which had received 5 c.c. of benzol every second day for three weeks and was then allowed to live for three weeks, the spleen measured:

Length.		Circumference.		Width.		Depth.
13	x	9.5	x	3	x	3.5 cms.

The last leukocyte count made on this animal was 7800 cells per cmm. three weeks before its death. The later counts through carelessness were not done. In the substance of the head of this spleen was a large hemorrhage. Splenic tumors measuring 9 cm. in length and over were found in 30 per cent. of the cases receiving benzol inhalations. In all these spleens there was the complication of miliary tuberculosis, so that the microscopic study cannot be reported on until control animals without tuberculosis have been treated with benzol in the same way.

Fatty Degeneration. In the kidneys, liver and heart muscle there were quite extensive fatty changes in gross and microscopic sections, stained with Sudan III. What the division of responsibility for this change between the benzol and tuberculosis is, we are unable to say at this time.

Bone Marrow. The diminution in the bone marrow of certain polymorphonuclear cells with neutrophile and basophilic granules is very constant and striking. Here again on account of the presence of tuberculosis in the animals and our lack of knowledge of rabbit bone marrow cells, we hesitate to speak positively. Comparing the bone marrow of the tuberculous animal with the benzol treated tuberculous animal, the striking feature, however, is the absence of the neutrophile polymorphonuclear cell. The eosinophile cell which is so very abundant in the rabbit marrow seems quite unaffected by the benzol.

Tuberculous Lesions. In all the treated animals the tuberculous lesions were much farther advanced than in the control animals. This difference was so constant that the variation could not be ascribed to difference in dose of organism, resistance of individual, or virulence of organism. The greater seriousness of the infection was apparent not only in the size and number of the tuberculous lesions, but in their confluence, caseation, and abscess formation.

It has seemed to us, from the microscopic study of these lesions, that fibrosis had proceeded to a greater degree in the treated animals, and that if the animals had been allowed to live longer than six weeks there might have been evidenced some greater resistance to the tubercle infection. Whether to ascribe the reduced resistance to the interference with the blood forming organs, to increased secretion, or activity on the part of the spleen; or to direct action of the benzol on the tubercle bacilli, we are quite unprepared to say. It does, however, seem that with the further study of this rather specific poison we may get a little nearer the solution of some of the unsolved problems of infection and immunity.

THE REMOVAL OF CALCIUM FROM THE BLOOD BY DIALYSIS IN THE STUDY OF TETANY

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AND
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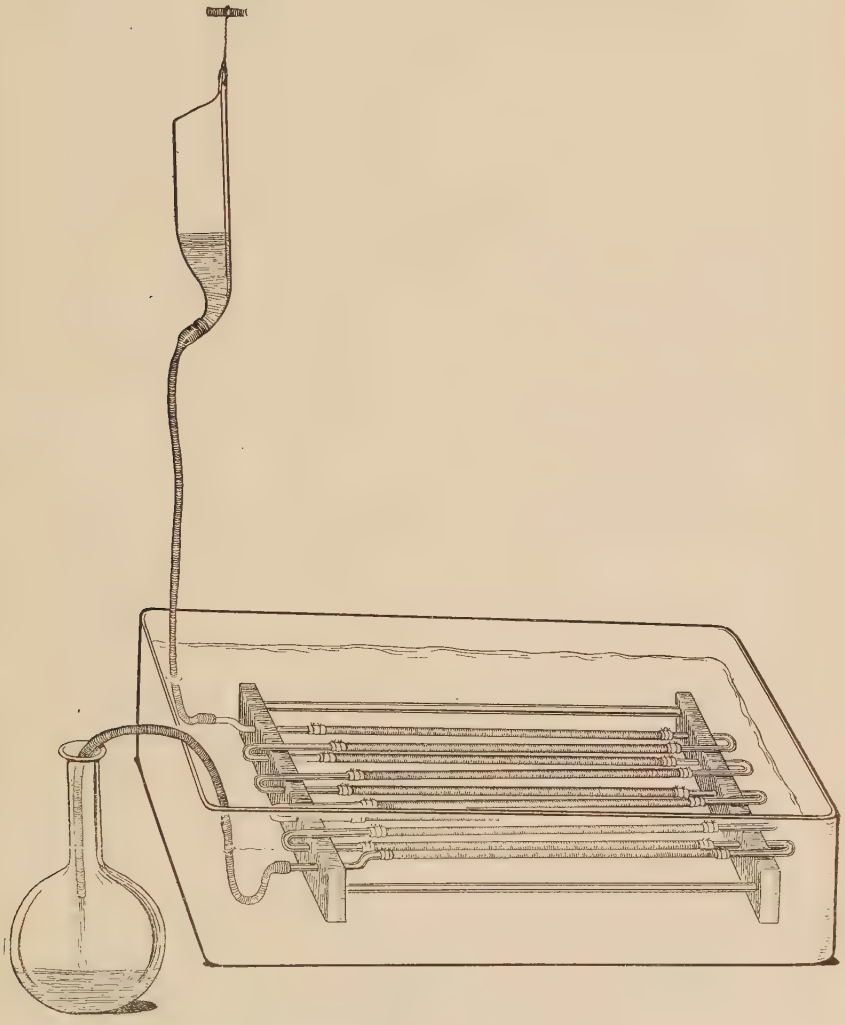
On the appearance of the paper by Abel, Rowntree, and Turner[1] describing a method by which diffusible substances might be removed from the circulating blood by dialysis, it occurred to us that we might attack the question of the relation of calcium salts to tetany in a new way.

At first we thought that we might be able to produce tetany by mechanically removing calcium from the blood by allowing it to circulate through celloidin tubes immersed in an isotonic solution containing no calcium. We therefore constructed a machine somewhat like Abel's, and made a number of experiments with this object in view, using a fluid put together according to Abderhalden's analysis of the inorganic constituents of the dog's blood, but without calcium. We varied this fluid by substituting phosphates for chlorides, with the idea that by removing chlorides also we might still further reduce the proportion of soluble calcium. We used defibrinated blood instead of salt solution in starting the current, and finally defibrinated all the animal's blood. The results were practically negative, and we abandoned the method because it seemed that we could attain our end better in another way without exposing the animal to an operation which must be prolonged over many hours.

We adopted a method which consisted in passing a quantity of

[1] Jour. Pharmacol. and Exper. Therap., 1914, v, 275.

defibrinated blood from another dog through a modified dialyzing apparatus (Text-figure 1) for many hours until, as we could ascer-



TEXT-FIG. 1.—Dialysis apparatus of celloidin tubes in series.

tain by chemical analysis, the amount of calcium was greatly reduced and had passed over into the dialyzing fluid. It was

then proposed to run the blood into the veins of a normal animal after an equal amount had been removed from the carotid artery, but even before this was done, it was thought best to ascertain the effect of the dialyzed blood upon the nerves of an isolated extremity by perfusion, according to the method previously employed[1] in studying the blood of animals in tetany. A number of experiments made in this way gave the following results.

Dog 1,420.—Normal extremity. Perfusion started at 3.50 P.M. with blood dialyzed against calcium-free fluid.

	2.00	3.30	3.50	4.00	4.10	4.20	4.40	4.50
KC[2]	0.2	0.05	Perfusion	0.05	0.05	0.05	0.1	0.2
KO	—[3]	—	started.	1.8	0.6	1.2	1.6	2.4
AC	0.5	1.0		0.2	0.5	0.6	0.4	1.2
AO	1.4	0.4		0.5	0.5	0.6	0.4	1.2

Blood used in perfusion contained calcium per 1,000 c.c. as follows:

Before dialysis.	After dialysis.	After perfusion.
0.085	0.0465	0.080

Dog 1,421.—Normal isolated extremity. Perfusion started at 4.15 P.M. in the same way.

	3.50	4.00	4.15	4.20	4.30	4.45	5.00	5.15	5.30
KC	0.4	0.6		0.2	0.4	0.4	0.4	0.4	0.4
KO	—	—	Per-	1.6	2.8	1.8	1.8	2.6	1.6
AC	1.0	1.6	fusion.	1.2	1.0	1.0	1.2	1.0	1.0
AO	1.2	2.0		1.2	1.0	1.0	1.0	0.8	1.0

Dog 1,427.—Normal leg perfused first with normal then with dialyzed blood.

	8.45	9.00	9.30	9.45	9.50	10.00	10.10	10.15	10.20	10.30	10.40	10.50	11.00	11.10	11.20	11.30	11.35	11.50
KC	0.3	0.4	Perfusion complete Normal blood	0.6	0.8	0.8	1.0	1.0	0.6	0.6	0.6	0.6	0.8	0.8	1.0	1.0	2.0	1.2
KO	—	—		—	—	—	—	—	4.4	3.6	4.0	3.4	3.4	—	—	—	—	—
AC	1.6	1.6		2.4	2.4	2.4	2.8	2.4	2.0	2.0	2.0	2.0	2.2	2.2	2.4	3.4	3.4	4.0
AO	1.8	2.4		—	4.6	4.6	3.2	2.6	2.0	2.0	2.0	2.0	2.0	1.4	2.4	2.2	2.6	4.0

↓ Dialyzed blood ↓ Normal blood

[1] W. G. MacCallum, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, xxv, 941.
[2] KC = kathode closing; AO = anode opening, etc.
[3] In all the tables — indicates negative up to 5 milliamperes.

It will be seen from these tables that the results of perfusion with dialyzed blood were not especially striking, nor do they convince one that the alterations in excitability of the nerves are strictly due to the withdrawal of calcium. From long previous experience, although it is known that a rise in excitability of a brief and temporary nature can come about from inadequacy of the circulation and that the great fall at the end of each curve is doubtless due to this or to some direct injury of other kinds, still it is also known that with a good circulation with normal blood the excitability will remain almost constant. These curves were especially inconclusive in that while a visible contraction could be elicited with weak currents, strong shocks gave only about the same muscular jerk. Instead of a brisk sharp contraction the foot moved lazily, often twisting in a peculiar way, and after the perfusion with dialyzed blood had gone on for only a short time peripheral contractions disappeared and the shock produced only jerking of the thigh muscles behind the electrode. These are inevitable signs of approaching death of the nerve, impressing us rather as the consequences of some sort of poisoning, and in every case the dialyzed blood was quickly exchanged for normal blood, sometimes with a return of the excitability.

Discouraged by these results, we determined to add the normal amount of calcium to our dialyzing fluid, which at this time had the following composition:

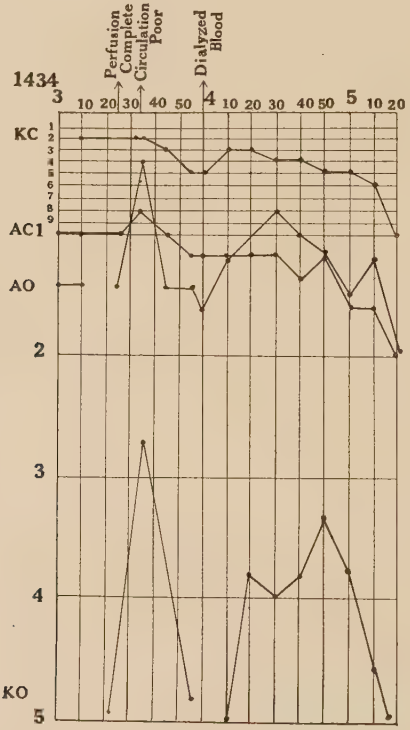
Sodium chloride	60.0
Disodium phosphate	28.5
Potassium chloride	4.0
Magnesium chloride	2.87
Sodium bicarbonate	5.0
Dextrose	10.9
Water	10,000

It became apparent at once, as we might have foreseen, that the calcium is precipitated by the phosphates present. Phosphates were therefore left out and calcium was added. After dialysis with this fluid, perfusion of the leg gave almost the curve which one would expect with normal blood.

Dog 1,434.—(Text-figure 2.) Normal leg perfused with blood dialyzed against a fluid containing calcium but no phosphates.

Sodium chloride	60.0
Sodium bicarbonate	5.0
Potassium chloride	4.0
Magnesium chloride	2.3
Dextrose	11.0
Calcium lactate	6.0
Water	10,000

	3.10	3.25	3.35	3.45	3.55	4.00	4.10	4.20	4.30	4.40	4.50	5.00	5.10	5.20
KC	0.2		0.2	0.3	0.5	0.5	0.3	0.3	0.4	0.4	0.5	0.5	0.6	0.1
KO	—	Per-	2.8	—	—	—	5.0	3.8	4.0	3.8	3.4	3.8	4.6	6.0
AC	1.0	fusion	0.8	1.0	1.2	1.2	1.2	1.2	1.2	1.4	1.2	1.6	1.6	2.0
AO	1.4		0.4	1.4	1.4	1.6	1.2	1.0	0.8	1.0	1.2	1.6	1.2	2.0

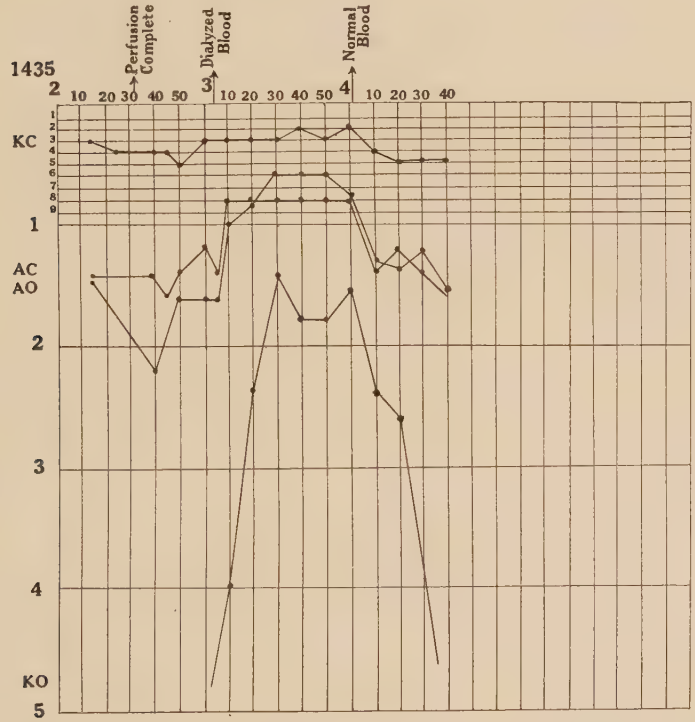


TEXT-FIG. 2.—Perfusion of leg with blood dialyzed against fluid containing all inorganic constituents of blood, including calcium.

It will be seen from Text-figure 2 that during the perfusion of normal blood a partial clamping-off of the supply tube produced a

brief rise in excitability which then passed away when the current was turned on in its full strength.

Therefore, from that point the experiments were begun again with a dialyzing fluid containing neither calcium nor any considerable quantity of the disturbing phosphates. Probably with this fluid the blood lost some of its phosphates, but the difficulty of devising a dialyzing fluid which should remove nothing but calcium from the blood seemed insurmountable.[1]



TEXT-FIG. 3.—Perfusion of leg with blood dialyzed against fluid devoid of calcium.

Dog 1,435.—(Text-figure 3.) Normal leg perfused at 2.32 P.M. with normal blood, at 3.01 with dialyzed blood, and at 4.01 again with normal blood. 900 c.c. of normal blood were dialyzed for 7½ hours against 18,000

[1] Since writing this paper it has been suggested to us by Dr. A. E. Taylor that as the phosphates in the blood are in non-dialyzable combinations there is little source of error in using a dialyzing fluid without phosphates.

c.c. of fluid (fluid 3) of the following composition, which was used in all later experiments.

Sodium chloride	60.0
Sodium bicarbonate	5.0
Magnesium chloride	2.3
Potassium chloride	4.0
Dextrose	10.9
Water	10,000

	2.15	2.18	2.32	2.40	2.45	2.50	3.00	3.05	3.10	3.20	3.30	3.40	3.50	4.00	4.10	4.20	4.30	4.40
KC	0.3	0.4	Perfusion complete	0.4	0.4	0.5	0.4	0.3	0.3	0.3	0.3	0.2	0.3	0.2	0.4	0.5	0.5	0.5
KO	—	—		—	—	—	—	—	4.0	2.4	1.4	1.8	1.8	1.6	2.4	2.6	—	4.0
AC	1.1	0.8		1.4	1.6	1.4	1.2	1.4	0.8	0.8	0.8	0.8	0.8	0.8	1.4	1.2	1.4	1.6
AO	1.4	1.0		2.2	2.0	1.6	1.6	1.6	1.0	0.8	0.6	0.6	0.6	0.8	1.4	1.4	1.2	1.6

↓ Dialyzed blood ↓ Normal blood

Dog 1,438.—(Text-figure 4.) Normal leg perfused at 4.20 P.M. with normal blood. This was changed to dialyzed blood at 5.02, and again to normal blood at 6.12. The dialyzed blood was 1,000 c.c. which had been poured through the long celloidin tubules for 7 hours against 24,000 c.c. of the fluid described above.

	4.00	4.20	4.25	4.30	4.40	4.50	5.00	5.05	5.10	5.20	5.30	5.40	5.50	6.00	6.10	6.20	6.30	6.40	6.50	7.00	7.10
KC	0.4	Perfusion complete	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.05	0.05	0.1	0.2	0.2	0.3	0.4	0.6
KO	—		—	—	—	—	—	—	—	—	1.0	0.6	0.4	0.5	0.3	0.4	0.5	0.8	1.2	1.8	3.6
AC	1.4		0.4	0.6	0.5	0.5	0.5	0.8	0.8	0.4	0.2	0.5	0.2	0.2	0.2	0.3	0.4	0.5	1.0	1.2	1.4
AO	1.4		0.6	0.3	0.4	0.6	0.7	0.8	0.8	0.4	0.2	0.2	0.2	0.1	0.1	0.2	0.3	0.3	0.6	1.0	1.2

↓ Normal blood ↓ Dialyzed blood ↓ Normal blood

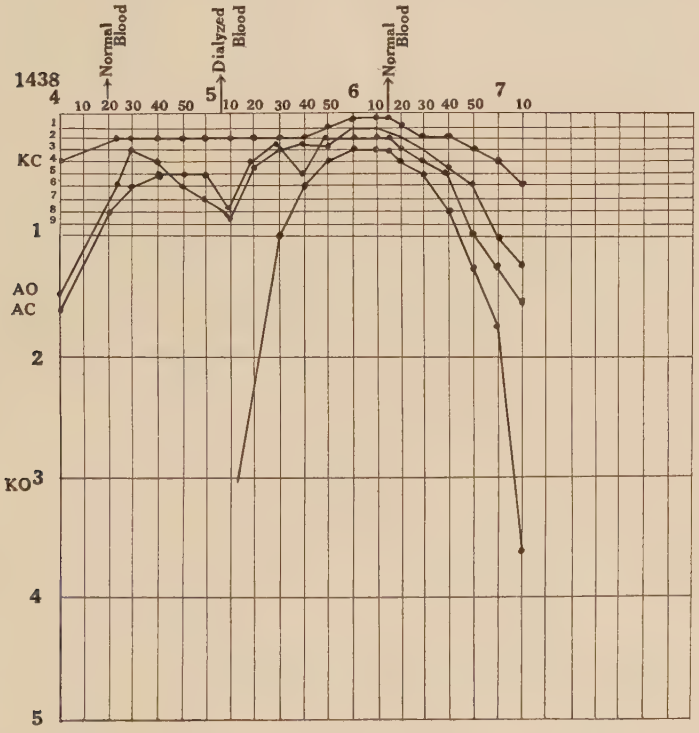
On the entrance of the dialyzed blood the leg jerked and moved itself about. Twitchings were evident until about 5.20.

The chemical analysis of the dialyzing fluid before and after dialysis, and of the blood at various points in the experiments, is as follows. The figures show the amount of calcium per 1,000 c.c.

	Dog 1,435.	Dog 1,438.
Dialyzing fluid before dialysis of blood	0.0040	0.0043
Dialyzing fluid after dialysis of blood (1st)	0.0076	0.0076
Dialyzing fluid after dialysis of blood (2d)	0.0048	0.0054
Blood before dialysis	0.0364	0.0442
Blood after dialysis	0.0284	0.0233
Blood after perfusion of leg	0.0212 (?)	0.0300

Text-figures 3 and 4 show clearly that perfusion with blood partly deprived of its calcium by dialysis produces great hyperex-

citability of the nerves, and further that this must be due solely to the loss of calcium, since exactly the same procedure, changed only by the addition of precisely enough calcium to the dialyzing fluid to prevent any loss or gain of calcium by the blood, brings



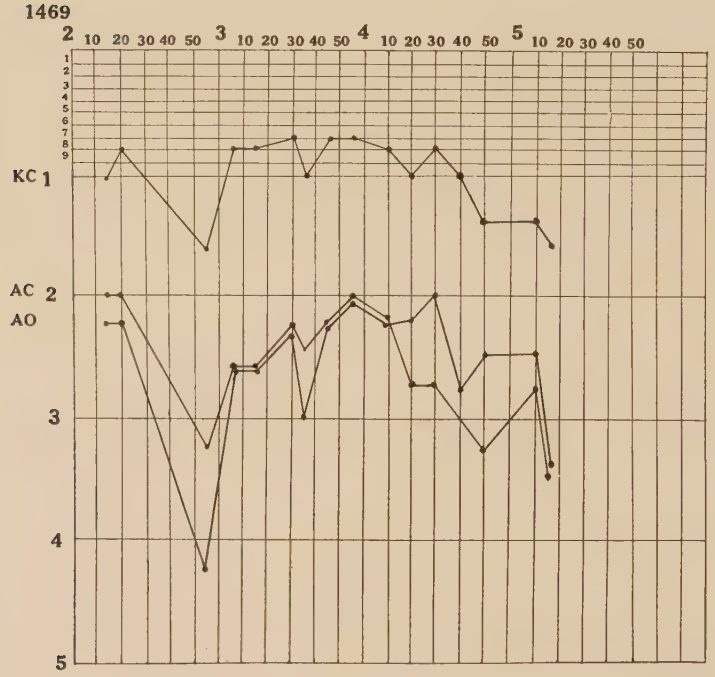
TEXT-FIG. 4.—Perfusion of leg with blood dialyzed against fluid devoid of calcium.

about no such hyperexcitability of the nerves. This proof may be somewhat strengthened by the addition of another curve made in the same way, except that the dialyzing fluid was so devised as to remove a large part of the chlorides from the blood, leaving the calcium unchanged.

Dog 1,469.—(Text-figure 5.) Normal leg perfused at 2.45 P.M. with normal blood, and at 3.30 with dialyzed blood. Dialysis was of 800 c.c.

of normal blood for $6\frac{1}{2}$ hours against 30,000 c.c. of fluid 4 of the following composition:

Sodium acetate	50.0
Sodium nitrate	40.0
Sodium bicarbonate	10.0
Magnesium chloride	2.3
Potassium nitrate	5.25
Calcium lactate	5.0
Dextrose	20.0
Water	10,000

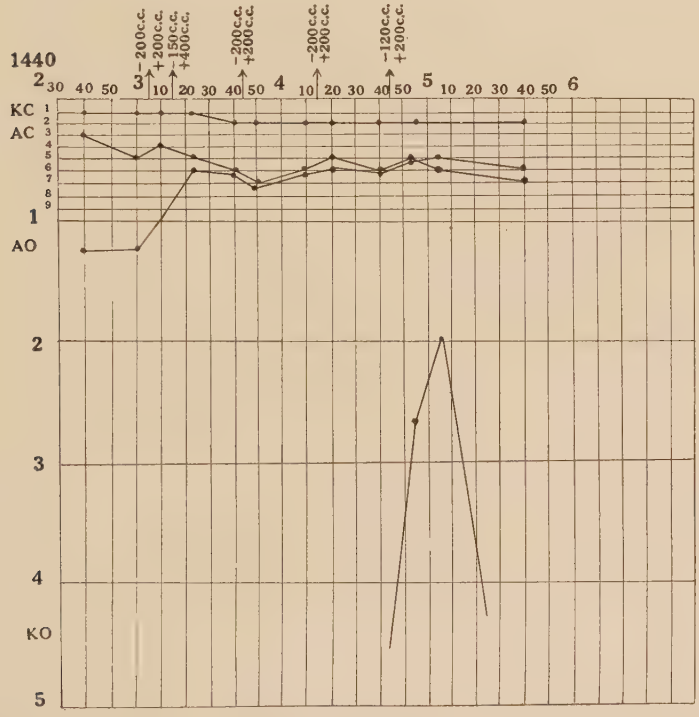


TEXT-FIG. 5.—Leg perfused with blood dialyzed against a chloride-free fluid.

	2.15	2.20	2.45		2.55	3.05	3.15	3.30	3.35	3.43	3.55	4.10	4.20	4.30	4.40	4.50	5.10	5.15
KC	1.0	0.8			1.6	0.8	0.8	0.7	1.0	0.7	0.7	0.8	1.0	0.8	1.0	1.4	1.4	1.6
KO	—	—	Per-	Normal	—	—	—	—	—	—	—	—	—	—	—	—	—	—
AC	2.0	2.0	fu-	blood	3.2	2.6	2.6	2.2	2.4	2.2	2.0	2.2	2.8	2.8	3.0	3.2	2.8	3.4
AO	2.2	2.2	sion.		4.2	2.6	2.6	2.2	3.0	2.2	2.0	2.2	2.2	2.0	2.8	2.6	2.6	3.4

↓ Dialyzed blood

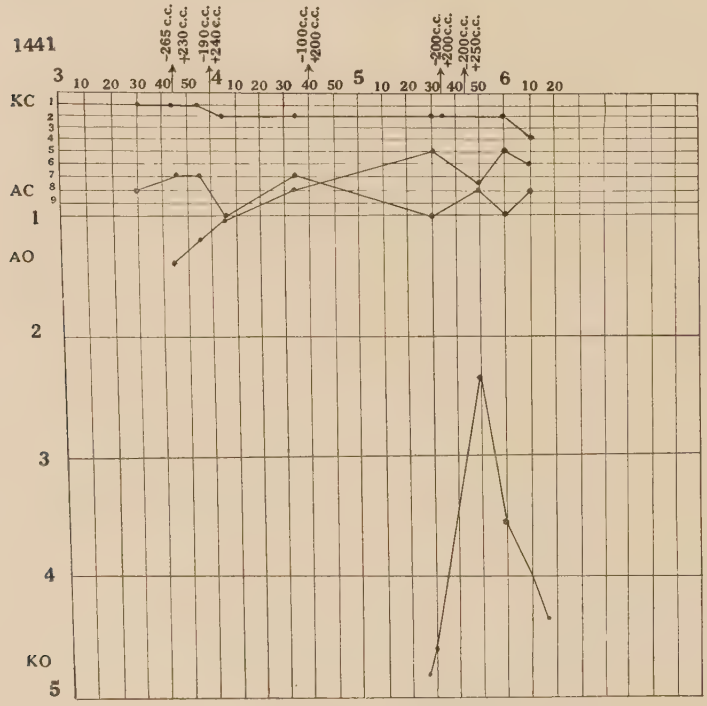
It is seen from Text-figure 5, in which the variations are so slight, that hyperexcitability of the nerves is not produced by long perfusion, even with blood greatly altered by dialysis, so long as the dialysis has not removed the calcium. When the calcium is diminished, however, the effect in producing hyperexcitability is prompt and persists as in the case of tetany blood so long as blood altered in this way is passing, giving way to normal conditions as soon as normal blood is again circulated.



TEXT-FIG. 6.—Repeated bleeding from carotid with replacement of blood dialyzed until poor in calcium

When an isolated extremity is perfused the influence of the undiluted dialyzed blood must be felt by the nerves, since there is but little tissue from which calcium or other constituents could be absorbed in the passage of the blood. We thought, therefore, that

this might be the most trustworthy expression of the nature of the influence of the dialyzed blood. Nevertheless we attempted to introduce dialyzed blood in quantity into the veins of an animal, realizing that it would at once meet with an abundant source of calcium in the tissues, but hoping to circulate it so rapidly as to surprise the nervous system and produce some hyperexcitability



TEXT-FIG. 7.—Normal animal. Blood replaced at intervals with dialyzed blood

not only of the peripheral nerves but of the ganglion cells. We planned not only to wash out all the animal's blood with dialyzed blood but to replace that, too, with fresh dialyzed blood. Indeed, after one or two experiments we even circulated fresh dialyzed blood through the whole animal, so that if the tissues were to supply calcium to all the new blood presented to them they must furnish enough to bring back to normal the calcium of five or six times as

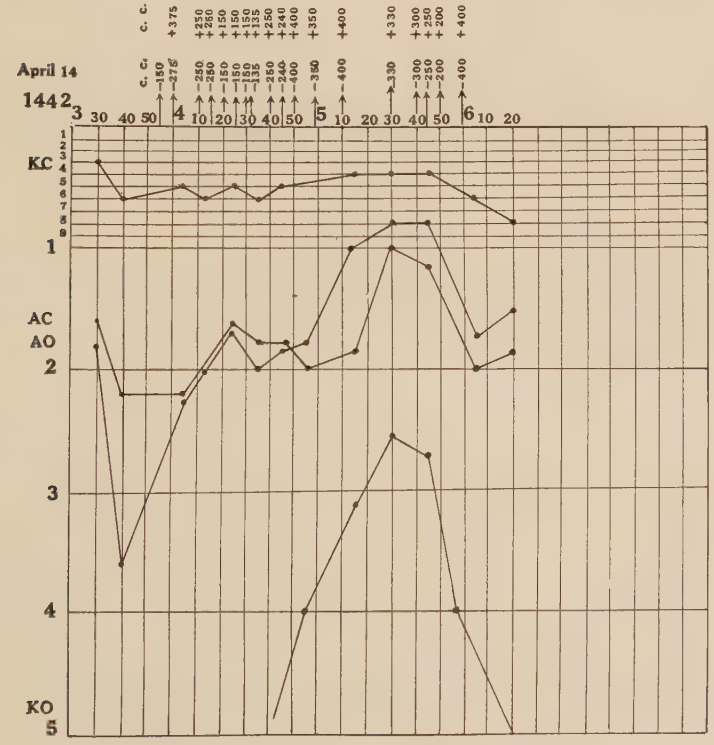
much blood as was passed by the animal before. At the beginning of each experiment the parathyroids of the animal were removed. The protocols are as follows:

Dog 1,440.—(Text-figure 6.) Normal animal bled at intervals, dialyzed blood being returned. Thyroids and parathyroids removed at 4.35 P.M. No tetany developed.

	2.40	3.00	3.10	3.25	3.40	3.50	4.10	4.20	4.45	4.55	5.05	5.40
KC	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
KO	—	—	—	—	—	—	—	—	—	2.6	2.0	—
AC	0.3	0.5	0.4	0.5	0.6	0.7	0.6	0.5	0.6	0.5	0.6	0.7
AO	1.2	1.2	1.0	0.6	0.6	0.7	0.6	0.6	0.6	0.5	0.5	0.6

Bled 200 c.c. 150 c.c 200 c.c 120 c.c.
Returned dialyzed blood. 200 c.c. 400 c.c. 200 c.c. 200 c.c.

In this experiment 1,350 c.c. of blood dialyzed for 7 hours against 30,000 c.c. of fluid 3 were used in replacing normal blood. Effect very slight.



TEXT-FIG. 8.—Normal animal through which dialyzed blood was actually circulated.

Dog 1,441.—(Text-figure 7.) Normal animal, blood at intervals replaced with dialyzed blood. 1,330 c.c. of blood dialyzed for 7½ hours against 26,000 c.c. of fluid 3. Parathyroids were removed just before the experiment started.

	3.30	3.45	3.55	4.05	4.35	5.30	5.50	6.00	6.10
KC	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.4
KO	—	—	—	—	—	4.6	2.4	3.6	4.0
AC	0.8	0.7	0.7	1.0	0.7	1.0	0.8	1.0	0.8
AO	1.4	1.4	1.2	1.0	0.8	0.5	0.8	0.5	0.6
Bled			265 c.c.	190 c.c.		200 c.c.	200 c.c.		
Returned dialyzed blood.			230 c.c.	240 c.c.		200 c.c.	250 c.c.		

There is general twitching; no definite tetany; much vomiting.

Dog 1,442.—(Text-figure 8.) Normal animal through whose bloodvessels dialyzed blood was actually circulated, as shown in the chart. Parathyroids first removed.

	3.20	3.40	4.05	4.12	4.25	4.35	4.45	4.55	5.15	5.30	5.45	6.05	6.20
KC	0.3	0.6	0.5	0.6	0.5	0.6	0.5	0.5	0.4	0.4	0.4	0.6	0.8
KO	—	—	—	—	—	—	—	4.0	3.2	2.6	2.8	4.0	5.0
AC	1.6	2.2	2.2	2.0	1.6	1.8	1.8	2.0	1.8	1.0	1.2	2.0	1.8
AO	1.8	3.6	2.2	2.0	1.6	2.0	1.8	1.8	1.0	0.8	0.8	1.8	1.6
Bled		150 c.c.	275 c.c.	250 c.c.	250 c.c.	150 c.c.	150 c.c.	135 c.c.	250 c.c.	240 c.c.	400 c.c.	350 c.c.	400 c.c.	330 c.c.	300 c.c.	250 c.c.	200 c.c.	400 c.c.	
Returned dialyzed blood.		375 c.c.		250 c.c.	250 c.c.	150 c.c.	150 c.c.	135 c.c.	250 c.c.	240 c.c.	400 c.c.	350 c.c.	400 c.c.	330 c.c.	250 c.c.	250 c.c.	200 c.c.	400 c.c.	

1,800 c.c. of blood dialyzed for 7 hours against 30,000 c.c. of fluid 3 were used. Each part of this probably circulated two and one-half times. Vomiting; no definite twitching; collapse and death.

From these experiments it seems clear that it is impossible in a short time to reduce the calcium content of the blood circulating through the whole body or to keep it reduced to such a degree as to bring about a tetany-like hyperexcitability of the nerves. There is too abundant a source for fresh calcium in the various tissues, including the bones, and the blood quickly replenishes itself. It might seem possible to repeat this process during several days and thus imitate the latent period which follows extirpation of the parathyroids, but in this case it would be necessary to extirpate those glands, when tetany would arise of itself, since otherwise the blood would rapidly replenish its calcium, under their influence, from the skeleton. Indeed, the rapidity with which calcium enters

the circulating dialyzed blood from the tissues is shown by comparison of the analyses of samples taken before and after its circulation in the body.

In dog 1,441 the blood contained per 1,000 c.c.:

Before dialysis	0.0485
After dialysis	0.0190
After circulation for about 2 hours	0.0381

It remains a question whether, if one could continue this depletion over several days, it would be possible to produce such changes in excitability as are seen in tetany, and in fact this was our original problem. It leaves one with the impression that the parathyroid secretion must govern the conversion of a non-dialyzable and useless combination of calcium into a dialyzable form which is essential for the control of the excitability of the nerves, but which is lost in the excreta and not newly formed in the absence of parathyroid secretion.

Although we had learned that it is possible by perfusion with calcium-poor blood to produce hyperexcitability of the nerve, it remained to bring this fact into direct relation with the condition in tetany, for it might be objected that there the mechanism is a different one. This we thought would be attained if we could show that this dialyzed blood had lost the power possessed by normal blood of curing tetany on transfusion. It is well known that if an animal in tetany, after the removal of the parathyroids be bled and the blood replaced with normal blood, the excitability of the nerves falls, and twitchings disappear for a time. Dialyzed blood poor in calcium has little or nothing of this effect, although if the dialyzed blood be not so poor in calcium as that of the animal in tetany, it will lower the excitability somewhat. If in an animal in tetany we replace the blood with dialyzed blood and find no change in the symptoms nor lowering of the excitability, we may remove that blood and replace it with normal blood which does stop the twitching and lower the excitability.

But if, although the excitability is not lowered by the dose of dialyzed blood, we do nothing further, the excitability is found to be lowered the next day or after some hours. To explain this we have imagined that while in dialysis we remove the calcium from

the normal blood, we may not remove the parathyroid secretion which on being injected into a dog in tetany after a time causes the appearance of dialyzable calcium in the blood and goes far to relieve temporarily the tetany. It is on this basis that it seems hopeless to attempt to produce a condition resembling tetany by the repeated replacement of the blood over a period of days with normal blood dialyzed until it is poor in calcium, because at the same time we furnish parathyroid secretion which ensures the continual withdrawal of calcium from the tissues. It is true that we might dialyze tetany blood, but even then having a blood free from parathyroid secretion and poor in calcium we have no animal in which to make evident the effect of pure lack of calcium, for the animal with intact parathyroids will continually frustrate this object, and the animal deprived of parathyroids will develop tetany during the experiment.

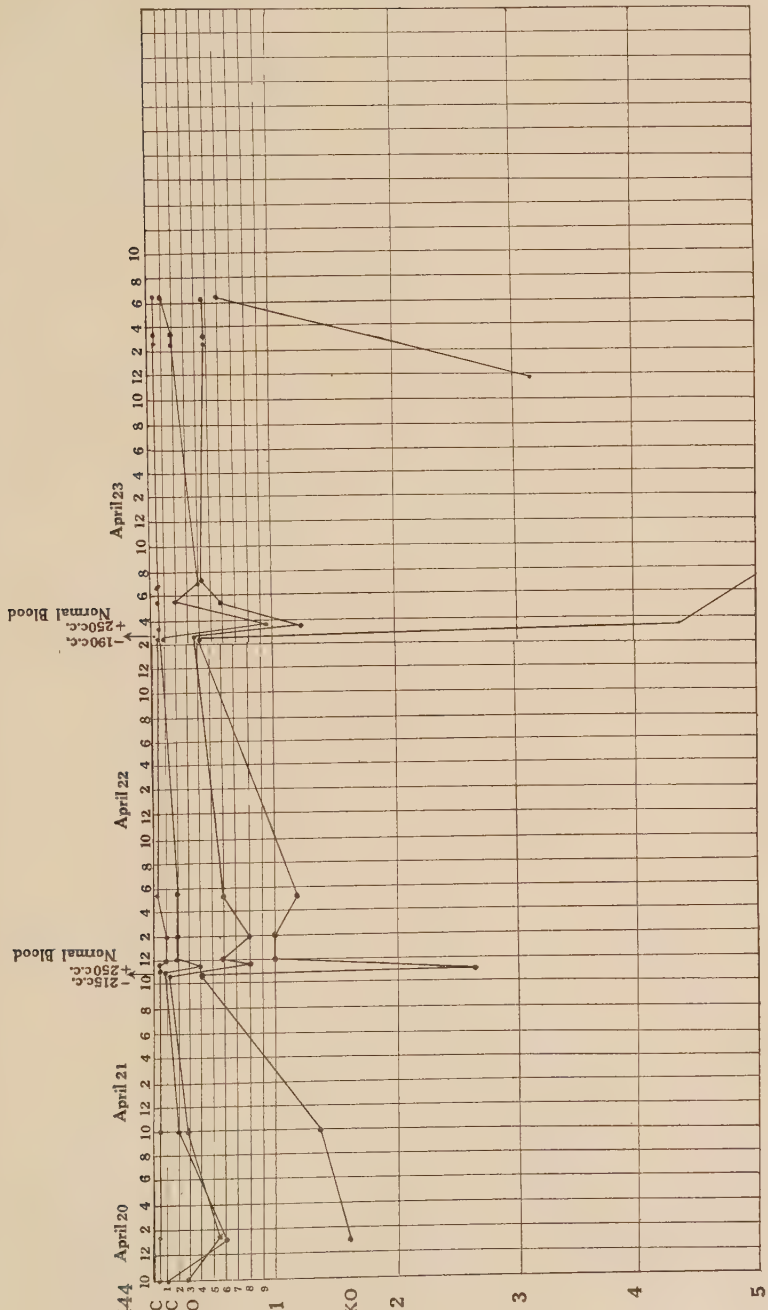
ILLUSTRATIVE PROTOCOLS

Dog 1,444.—(Text-figure 9.) Tetany developing 2 days after parathyroidectomy. Bled on two occasions, normal blood being replaced. Transient relaxation and lowering of excitability.

	April 20.		April 21.						April 22.				April 23.		
	10.00	1.45	10.00	11.15	11.40	12.00	2.00	5.45	2.30	2.55	5.30	6.35	2.20	3.10	6.30
KC . .	0.05	0.05	0.05	0.05	0.05	0.1	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
KO . .	....	1.6	1 4	0.4	2.6	1.0	1.0	1.2	0.4	4.4	—	—	—	—	0.6
AC . .	0.1	0.6	0.2	0.05	0.05	0.4	0.2	0.05	1.0	0.2	0.4	0.2	0.2	0.2	0.1
AO . .	0.3	0.6	0.3	0.1	0.8	0.6	0.8	0.6	0.4	1.2	0.6	0.4	0.5	0.5	0.5
					↓				↓						
Bled					215 c.c.				190 c.c.						
Returned normal blood					250 c.c.				250 c.c.						

Dog 1,451.—(Text-figure 10.) Violent tetany 24 hours after parathyroidectomy. Bled 800 c.c., and this loss was replaced by 625 c.c. of normal blood. Immediate relaxation and lowering of excitability of nerves.[1]

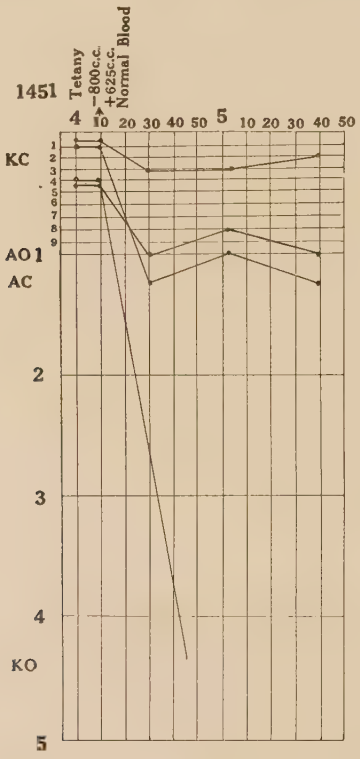
[1] A curious phenomenon was observed in these cases in which nearly all the blood was removed, at the moment before the normal blood was allowed to run in. Although twitching may have been slight when the bleeding began, the most violent contractions and extreme rigidity appeared during the extreme anemia, to disappear at once when the other blood entered the veins. Probably this is due to temporary asphyxia of the nerves.



Text-fig. 9.—Tetany. Bled on two occasions; normal blood replaced. Transient effect.

	April 26.					April 27.	April 28.
	4.00	5.00	5.20	5.55	6.30	11.00	12.15
KC	0.05		0.3	0.3	0.2	0.1	0.05
KO	0.4	Blood	—	—	—	—	0.3
AC	0.1	replaced	1.2	0.1	1.2	1.2	0.05
AO	0.4	by normal	1.0	0.8	1.0	1.2	0.2
		↓					↓
	Bled	800 c.c.					425 c.c.
	Returned normal blood	625 c.c.			Returned dialyzed blood		400 c.c.

This animal developed tetany again on April 28 and was bled 425 c.c., 400 c.c. of dialyzed blood being replaced. There was no recovery from the spasm brought on by the bleeding, and death followed rapidly. This case forms an example of the contrast between the effects of introducing normal and dialyzed blood.

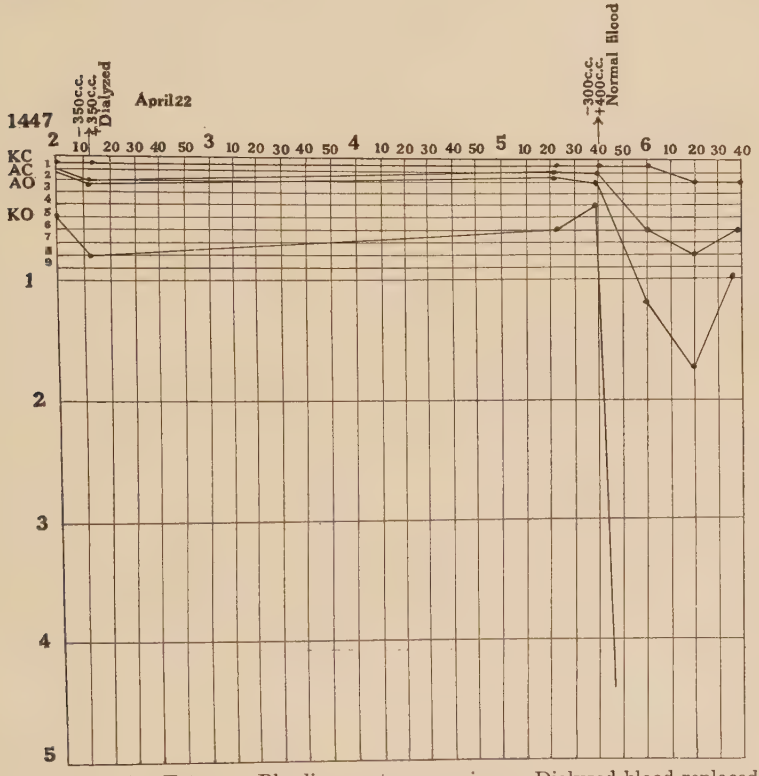


TEXT-FIG. 10.—Tetany. Effect of bleeding and replacing normal blood.

Dog 1,445.—Moderate tetany 2 days after parathyroidectomy. At 2.23 P.M. bled 150 c.c. Blood replaced by 150 c.c. of blood dialyzed for 5 hours against 10,000 c.c. of fluid 3. At 3.20 bled 150 c.c., and replaced 150 c.c. of normal blood. At 10.30 bled 200 c.c., and replaced 250 c.c. of normal blood.

	April 20.									April 21.						
	1.30	1.45	2.20	2.30	2.40	3.00	3.20	3.45	4.25	10.00	10.45	11.00	11.15	12.00	2 .00	5.45
KC	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.1	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
KO	0.2	0.3	0.3	0.3	0.4	0.3	0.6	1.4	0.6	0.2	0.4	0.4	0.4	— [1]	2.0	1.4
AC	0.05	0.1	0.05	0.05	0.05	0.05	0.1	0.2	0.1	0.05	0.05	0.1	0.1	0.1	0.2	0.3
AO	0.2	0.3	0.3	0.3	0.4	0.3	0.4	0.5	0.3	0.3	0.4	0.5	0.4	0.4	0.3	0.3

Bled 150 c.c. 150 c.c. 200 c.c.
Returned dialyzed blood 150 c.c.
Returned normal blood 150 c.c. 200 c.c.



TEXT-FIG. 11.—Tetany. Bleeding on two occasions. Dialyzed blood replaced without effect. Normal blood reduces excitability.

Dog 1,447.—(Text-figure 11.) Violent tetany at 2 P.M. Bled 350 c.c. which were replaced with 350 c.c. of blood from a lot of 600 c.c. which had been dialyzed for $4\frac{1}{2}$ hours against 12,000 c.c. of fluid 3. Change in character of electric reaction, but no marked change in excitability. Con-

[1] Negative up to 3 milliamperes.

traction slow, no rigidity. Tongue tremor and twitchings continue. At 5.45 bled 300 c.c., and replaced 400 c.c. of normal blood. Complete relaxation and return of excitability to normal.

	April 22.										
	11.45	2.00	2.15	2.55	5.25	5.40	6.00	6.00	6.45	9.00	12.00
KC	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.2	0.2	Quiet;	Twitching:
KO	0.5	0.5	0.8	Tongue and muscle	0.6	0.4	—	—	—	no tongue tremor	tremor in
AC	0.1	0.1	0.2	tremor	0.1	0.1	0.6	0.8	0.6		tongue.
AO	0.1	0.1	0.2		0.1	0.2	1.2	1.8	1.0		
		↓					↓				
Bled		350 c.c.					300 c.c.				
Returned dialyzed blood		350 c.c.				Returned normal blood	400 c.c.				

Dog 1,452.—No tetany 4 days after parathyroidectomy. Moderately high excitability. Bled 315 c.c., replaced by 330 c.c. of blood dialyzed 7 hours against fluid 3, $\frac{\text{430 c.c. blood}}{\text{10,000 c.c. fluid}}$. Animal much depressed and vomited. Excitability a little lowered, and this lowering continued and increased for the next two days. Then bled 300 c.c., which were replaced by 300 c.c. of blood dialyzed for 6 hours, $\frac{\text{400 c.c.}}{\text{15,000 c.c.}}$. No marked change in excitability.

	April 29.					May 1.				
	5.00	5.25	5.35	5.50	6.05	2.00	5.00	5.40	5.50	6.25
KC	0.05	0.2	0.2	0.2	0.1	0.2	0.1	0.2	0.2	0.1
KO	1.8	2.6	2.0	2.0	2.0	—	—	—	—	—
AC	0.4	0.8	0.8	1.2	1.0	1.4	1.2	1.2	1.2	1.2
AO	0.5	0.8	0.8	1.0	0.8	2.0	1.4	1.4	1.6	2.0
		↓					↓			
Bled		315 c.c.					300 c.c.			
Returned dialyzed blood		330 c.c.					300 c.c.			

We made a number of analyses of the blood of animals in tetany, of the dialyzed normal blood used to replace their own, of the normal blood, and of the normal or dialyzed blood removed again after it had circulated for a time in the animal, thinking that a comparison of these figures might throw some light on what occurred in the body to influence the tetany. But such figures would be difficult to interpret because they would change continually with

the time the new blood was allowed to stay in the body, first through the process of obtaining a balance with the tissues, and then through the same process that disturbed the composition of the blood to produce tetany. It might be expected then that thoroughly dialyzed blood left in a tetany animal would become richer in calcium for awhile, although normal blood introduced in the same way would steadily lose calcium until it became very poor indeed, when another attack of tetany might come on, as in dog 1,451.

If tetany blood be dialyzed under exactly the same conditions as normal blood, it still loses a proportionate amount of its calcium, which would perhaps show that it is not especially the loss of a diffusible calcium as contrasted with a non-diffusible form which is important in producing tetany. The blood of dog 1,451 taken during tetany contained 0.0287 of a gram of calcium per 1,000 cubic centimeters. 500 cubic centimeters dialyzed for 5 hours against 12,000 cubic centimeters of fluid 3 then contained 0.0114 of a gram per 1,000 cubic centimeters.

Conclusions. We may devise a fluid containing practically all the inorganic diffusible constituents of the blood except calcium, and use it to dialyze normal blood in such a way as to remove from it a large part of its calcium. The dialyzed blood when perfused through an isolated extremity produces an extreme hyperexcitability of the nerves quite like that observed in tetany. Since perfusion with blood dialyzed in precisely the same way against a fluid of the same composition, but containing calcium in the proportion found in the normal blood, causes no hyperexcitability of the nerves, it is evident that the hyperexcitability is due to the lack of calcium. This effect can be attained in only a slight degree by replacing the blood of a whole animal with the dialyzed blood, since under the conditions of the experiment the tissues cannot be sufficiently depleted of their calcium. It seems probable that the parathyroid secretion is not removed by dialysis, but is returned to the body with the dialyzed blood.

To bring this result into relation with the condition in tetany following parathyroidectomy, animals in tetany were bled and the blood was replaced in one case with normal blood, in the other with dialyzed blood poor in calcium. The normal blood immediately

relieves the tetany and lowers the excitability, while the dialyzed blood does not. We therefore believe that this is a further proof that in the tetany of parathyroidectomy also the twitching and hyperexcitability of the nerves is due to lack of calcium in the blood and tissues.

DISCUSSION

Dr. S. J. Meltzer: I would like to ask Dr. MacCallum whether the absence of phosphates may have been a factor in these cases.

Dr. MacCallum: I cannot tell with certainty from our experiments whether a loss of phosphates from the blood would affect the excitability of the nerves. The same query might arise about other substances, but since no hyperexcitability is produced when phosphates are omitted from the dialyzing fluid and calcium introduced, their influence must be negligible.

THE FUNCTIONAL EFFECT OF EXPERIMENTAL INTRASPINAL INJECTIONS OF SERUMS WITH AND WITHOUT PRESERVATIVES[1]

By JOHN AUER, M.D.
NEW YORK

A RIGID test of the therapeutic efficiency of the antimeningitis serum prepared by the Rockefeller Institute has demonstrated during the last six years that the former mortality of about 70 per cent. from epidemic meningitis can be so reduced by the appropriate use of this serum that the death rate now fluctuates between 25 and 30 per cent. Instead of about 70 per cent. deaths, approximately 70 per cent. recoveries are now observed; and in addition to this life-saving property, the antimeningitis serum can reduce the period of illness, and markedly lessen the appearance of serious chronic consequences of epidemic meningitis.[2] Nevertheless the question can be raised whether a fraction of these deaths, which still occur during the process of serum treatment, could not be attributed to the serum itself. At present, for all practical purposes this question must be considered of scientific interest only, and it must emphatically be kept in mind that the antimeningitis serum is the only effective remedy which we possess for this disease, and that it must be employed even if some deaths were caused directly by the serum itself. It must be clear to every physician that a treatment which yields about 70 per cent. recoveries in a disease which untreated kills 70 per cent. of those infected, cannot be abandoned because this treatment, perhaps, causes some fatalities.

[1] A preliminary communication was published in Jour. Amer. Med. Assoc., 1914, lxii, 1799.

[2] See the critical review of 1300 cases given by S. Flexner, Jour. Exp. Med., 1913, xvii, 553–576.

Just as obvious as the consideration mentioned is the one that every remedial agent should be perfected as far as possible, that every conceivable source of danger to the patient from the remedy itself should be carefully sought out and, if possible, removed. A few investigations of this character regarding antimeningitis serum have already been made and the present paper is an attempt in the same direction.

The main sources of danger to the organism during the repeated intraspinal administration of antimeningitis serum have been pointed out by Flexner[1] and are theoretically the following: anaphylaxis, the production of toxic products by the rapid lysis of meningococci, increased pressure in the cerebrospinal system, and intoxication from the phenol compounds often used to preserve the sera from accidental contamination. The last supposition is the one which has received the most attention, at least in this country. This focus upon the possibility that a poisoning by phenol compounds explained a number of fatalities during serum administration in meningitis is due to S. P. Kramer[2] who published a series of cases where death occurred after the administration of tricresol antimeningitis serum. Kramer attributes the fatal issue to a paralysis of the respiration caused by the tricresol preservative which reached the medullary centres through an opening in the conus medullaris connecting the spinal subdural space with the central canal of the cord. To support this hypothesis Kramer made a few experiments on dogs; he injected tricresol solutions into the vertebral artery, the subdural space of the posterior cranial fossa, and into the subdural space of the lumbar region. His experiments with intravenous injections need not be considered here because we are not dealing with the toxicity of tricresol when given in this way. The other two experiments, illustrated each by a blood-pressure and respiration tracing, showed that 2 c.c. of a 0.5 per cent. water solution of tricresol injected in the posterior cranial fossa caused a stoppage of the respiration and a fall in blood-pressure. Kramer states that artificial respiration was necessary for ten

[1] Jour. Amer. Med. Assoc., 1913, lx, 1937.

[2] Ibid., 1913, lx, 1348; Lancet-Clinic, 1913, cix, 304; Ibid., p. 357; Ibid., 1914, cxi, 509.

minutes before spontaneous respiration began. In the next experiment 2 c.c. of antimeningitis serum containing tricresol was injected into the lumbar subdural space of a young dog. A few seconds after the injection the respiration ceased but was restored partially by two short periods of artificial respiration. After this, artificial respiration was stopped and the animal died five minutes later.

These clinical experiences and experiments led Kramer to the conclusion that 0.5 per cent. tricresol serum cannot safely be injected into the subarachnoidean space. The same author[1] suggests that tricresol be replaced by a formalin-serum mixture of 1 to 1000, and supports this by an experiment which showed that 2 c.c. of 1 to 1000 formalin-serum injected into a vertebral artery of a dog produced but slight effects on the respiration and blood-pressure. It must be added that, according to Kramer,[2] the vertebral artery delivers its contents directly to the hind-brain without passing it through the circle of Willis.

The next paper dealing with this subject is by Flexner[3] who gives a critical consideration of those dangers which are referable to the serum itself. Flexner is not inclined to lay great weight on the suggestion of Kramer that the fatalities are due to tricresol intoxication. He points out that accidents have occurred after the employment of the Dopter antimeningitis serum which contains no preservative at all; that injection of tricresol serum into the lateral ventricles of the brain has caused no fatalities though the route which the tricresol serum could take to the medulla is surely a direct one; Flexner suggests, since the doses employed in the cases referred to by Kramer were generally maximal and were usually injected with a syringe, that increased cerebral pressure was the cause of respiratory failure in these unfortunate cases.

The next investigation is by Hale[4] and is an experimental study of the effect of tricresol serum upon the blood-pressure and respiration when injected intraspinally in dogs and cats. The dogs were anesthetized by 5 mg. of morphine per kilo weight given subcu-

[1] S. P. Kramer, Lancet-Clinic, 1913, cix, 357.
[2] Jour. Exper. Med., 1912, xv.
[3] Jour. Amer. Med. Assoc., 1913, lx, 1937.
[4] Hygienic laboratory Bulletin, 1913, No. 91.

taneously, and by 45 mg. ethyl carbamate and 18 mg. chloral hydrate per kilo given per os. The cats received no morphin but only the solutions of ethyl carbamate and chloral. Occasionally the anesthesia was aided by ether. It must be remarked that the hypnotics used by Hale are medullary depressants and in addition at least two of them, urethane and chloral, increase markedly the secretion of cerebrospinal liquid according to Dixon and Halliburton.[1] These two substances would thus tend to raise the intraspinal pressure. The blood-pressure was recorded from the carotid artery by a mercury manometer; the respiration was registered in a variety of ways, the final method being a cannula in the pleural cavity, connected with a tambour. For the main experiments laminectomy was performed because the results obtained by inserting the needle through the skin into the spinal dural sac were irregular.

The tricresol serum solutions were prepared by adding the requisite amount of tricresol (0.3 to 1 per cent.) to the anti-meningitis serum about one hour before the injection. Just before use the mixture was filtered and warmed. Hale used the syringe method.

The results obtained by Hale were briefly as follows: Following the injection of tricresol serum the respiration after a preliminary stimulation slowed markedly, decreased in depth, and stopped temporarily (p. 10). After a fatal amount of tricresol serum, death was preceded by a permanent paralysis of respiratory activity, though certain experiments showed respiratory gasps as long as the heart continued to beat (p. 14). The blood-pressure after tricresol serum often showed a slight initial rise, but in every instance it later fell below normal, while the heart rate was not much changed. After a toxic amount of tricresol serum the blood-pressure fell slowly to zero subsequent to the failure of the respiration (p. 14).

The amount of tricresol serum which caused death Hale found to be less than 2 c.c. of a 0.5 per cent. tricresol solution per kilo weight. With 0.3 per cent. solutions the fatal dose was "somewhat larger," with 1 per cent. "considerably smaller" (p. 14).

Hale states (p. 17) that normal serum never produced symptoms aside from those ascribed to increased cerebral pressure. The blood-pressure always shows an enormous rise of blood-pressure which

[1] Jour. Physiol., 1913–1914, xlvii, 238.

later rapidly falls to zero in the fatal cases; associated with this is a complete cessation of respiration. After tricresol serum the respiration falls but the "blood-pressure always falls" and does not show the tremendous rise obtained with serum alone. Moreover, tricresol serum was found much more toxic than the same serum free from preservative.

Hale concludes (p. 18) that his experiments substantiate Kramer's contention that tricresol is a dangerous preservative for sera which are to be brought directly into contact with the vital nervous centres, and that death may result either from an increase of intracranial tension or from the presence of tricresol in the serum. The danger from tricresol, however, according to Hale "seems much greater and more certain than that which may possibly arise from increased pressure." Hale suggests that an effort be made to discover a serum preservative which does not have the toxic action of tricresol on the central nervous system, and if that is not possible, to dispense the serum without any preservative in sterile containers.

The last paper on this subject is a short communication by Fitzpatrick, Atkinson, and Zingher.[1] These authors made a series of experiments in dogs by injecting tricresol and chloroform sera intravenously, intra-arterially, and into the lumbar subdural space. Only the latter experiments need be considered here. The injections were made through the skin, and laminectomy was not performed. They observed no marked disturbances of the blood-pressure in normal dogs after moderate doses of antimeningococcus sera containing 0.3 per cent. tricresol. Similar results were obtained when physiological salt solution, "old" antimeningococcus serum, antimeningococcus serum with 0.3 per cent. and 0.4 per cent. tricresol, normal horse serum, and various sera with chloroform were injected subdurally. They conclude that pressure appears to be a factor of real danger.

The investigation to be reported in the following pages was undertaken in order to study not only in dogs, but also in monkeys, the effects which are produced when normal sera or sera preserved by 0.3 per cent. tricresol, 0.3 per cent. chloroform, and 0.3 per cent. ether are injected into the lumbar subdural sac. The tricresol

[1] Proc. Soc. for Exp. Biol. and Med., 1914, xi, 182.

and chloroform sera were of 0.3 per cent. strength because the majority of the dog experiments and all of the monkey experiments were carried out with the antimeningitis sera furnished by the New York and Massachusetts Boards of Health and in these sera the preservatives are present in 0.3 per cent. strength.

Because of the opinions already expressed by various authors concerning the action of sera when injected intraspinally, the experiments made in this investigation will be given with some detail and they will be illustrated by curves which show the behavior of an animal during a fifteen-minute interval.

Experiments. *Method.* All experiments were carried out in dogs and monkeys (macacus rhesus). Both species of animals were kept under light ether anesthesia and the loss of body heat prevented or reduced by an electric pad upon which the animal was stretched out. The method of maintaining anesthesia as well as the preliminary operative interferences were, however, quite different in the dog and the monkey, although it was attempted to make the conditions of the experiments as similar as possible to those which prevail when the human subject receives an intraspinal injection of a therapeutic serum. It will be seen from the following descriptions that only in the monkey were the anatomical conditions such as to permit a close approximation to the procedure employed in human therapeutics.

The dog was always anesthetized by means of intratracheal insufflation, a procedure which not only permits the maintenance of a quite constant level of narcosis but which also prevents any danger from the stoppage of spontaneous respiration. In the monkey no intratracheal insufflation was attempted and the animal was etherized cautiously by the ordinary cone-drop method. The latter animal therefore received a varying amount of ether per unit of time due to the method, and the monkey was subject to asphyxia if the respiration should become shallow or fail. Tracheotomy was only performed in one series of dogs where local applications were made to the medulla.

Another wide divergence of procedure occurred in the process of injecting the alien serum subdurally. In the dog the ordinary method employed in the human being cannot be used with safety and certainty because the spinal cord of the dog unlike that of the monkey extends practically to the sacrum. If a hypodermic needle is introduced between the lumbar vertebral laminæ it is thus almost certain to wound the spinal cord, and this damage would be greatly increased if followed by an injection; if the needle insertion is made in the neighborhood of the sacrum there is little guarantee that the needle is really in the dural sac, for spinal fluid was

obtained only exceptionally by me no matter where the needle was introduced. These difficulties render an exposure of the spinal cord imperative even for moderately precise work of this type in the dog, and a laminectomy was therefore always performed in this animal. Hale also found a laminectomy necessary in the dog in order to secure uniform results.[1]

As a rule two lumbar vertebræ were removed, either the second and third or the third and fourth. After exposure of the dura, the wound was carefully covered with a fine layer of dry cotton to prevent oozing and the cavity was filled with a wad of cotton saturated with vaseline. The injection was made by means of a hypodermic needle bent at right angles. After preliminary puncture of the dural sac the needle was introduced and the dura gently lifted so that the injected fluid should not injure the cord. After the injection the needle was usually kept *in situ* for some seconds, then withdrawn and the puncture wound immediately covered firmly with the vaseline-soaked cotton plug, and this plug itself was kept applied by means of a light weight.

In the monkey, however, no such severe measures were necessary in order to give an intraspinal injection with certainty; here it sufficed to introduce a hypodermic needle between the laminæ of the lumbar vertebræ in order to tap the spinal dural sac. The appearance of spinal fluid in the cap of the hypodermic needle served as index of the proper location of the needle point. Under no circumstances was an injection ever given to a monkey before clear or only slightly blood-stained spinal fluid had been obtained. Occasionally, however, the amount of spinal fluid available apparently was too small to fill the hypodermic needle, which had a lumen of about 0.5 mm. Such a diminution of available spinal fluid seemed to occur especially in monkeys which had been injected some days previously, and was only exceptionally encountered in unused monkeys. Under these conditions a device was used to detect spinal fluid which was originated by Dr. Flexner; a sterile capillary glass tube was cautiously inserted into the needle; if fluid was present it rose at once in the tube and even formed a drop at the free end. It need hardly be stated that for this test the hypodermic needle must be inserted dry.

The site of injection in the monkey varied; usually the space just above the one at the level of the iliac crests was employed; if no fluid was obtained, then the space above or below the one mentioned was entered. Occasionally it happened that the first three attempts failed, but later trials in a space already tested now yielded cerebrospinal fluid, at times in abundance.

As the majority of the monkeys were reinjected after seven to fifteen minutes when graphic records of the blood-pressure and respiration were taken, the hypodermic needle tapping the spinal dural sac was allowed to remain *in situ* in the etherized monkey throughout the experiment. After cerebrospinal fluid had been undoubtedly obtained the cone-shaped

[1] Loc. cit., p. 11.

orifice of the cap was stoppered with a cork. Repeated intraspinal injections were thus rendered a simple matter, and only a slight loss of fluid took place before the stopper could be replaced.

The injections were always given by syringe and never by the gravity method. This was done in order to test the sera under conditions which obtain when an intraspinal injection is given by the average physician. It may be remarked here that there seems to be a general impression that the gravity method abolishes the danger of increased intraspinal pressure. This is not true unless the serum is absorbed as soon as injected, a condition which is probably never fulfilled. The pressure under which serum enters the dural sac must therefore always be greater in the gravity system than in the spinal dural sac for otherwise no serum would enter; in consequence the intraspinal pressure must also rise when the rate of infusion exceeds its rate of absorption, and the degree of this rise of intraspinal pressure depends entirely upon the operator.

The blood-pressure was always recorded by a mercury manometer, the tubing being filled with a half saturated solution of sodium sulphate. In the dog the left carotid artery was used, and in the monkey a femoral artery.

The respiration was written in both dogs and monkeys by means of a Meltzer pleural cannula which was inserted in the left pleural cavity and connected with a Marey tambour. The negative pressure was often reëstablished after the pleural cannula was fixed in place by distending the lung and then closing the cock of the cannula. Occasionally it happened that the cannula was improperly placed so that its orifice became plugged in some way or another; when this occurred a partial or even full unilateral pneumothorax was established in order to obtain a graphic record.

The following kinds of horse serum were injected: 0.3 per cent. tricresol antimeningitis serum (no other strength was tested), 0.3 per cent. chloroform antimeningitis serum, 0.3 per cent. ether horse serum. For the tricresol and chloroform antimeningitis sera I am under obligation to the New York and Massachusetts Boards of Health who placed liberal quantities of these sera at my disposal. The ether-serum was prepared by the addition of an appropriate amount of ether to the cold sterile horse serum in a tightly stoppered bottle which was then shaken and kept in the ice chest. Sterile horse serum without any preservative whatsoever and Ringer solution were also injected as controls. Practically none of the sera employed were freshly prepared. All were usually at least several weeks old before they were used for intraspinal injection. A few experiments, however, in the dog were made with normal horse serum to which 0.3 per cent. tricresol had been added, and this serum was used after a few days. In these experiments more severe effects on the blood-pressure and respiration were obtained than with 0.3 per cent. tricresol antimeningitis serum. As only a few experiments were made with this serum, it can merely be suggested that fresh tricresol

sera perhaps exert stronger effects upon the medullary centres than older solutions.

The usual amount injected each time was 5 c.c. in the dog and 3 c.c. in the monkey. In the dog a certain leakage always occurred after the second injection through the puncture made in the dural sac by the hypodermic needle. This leakage was reduced by immediately covering the puncture and exposed dura with a vaseline-cotton plug. In the monkey a slight subcutaneous leakage from the dural sac was observed only once.

The dose injected per kilo animal ranged from 2 to 6 c.c. for both dogs and monkeys. It must be observed that this method of calculating the amount of serum injected intraspinally is not a good one, for the size of the dural sac by no means increases in the same ratio as the weight of the dog. If thus two grown dogs of 5 and 10 kilos weight received each 25 c.c. of serum intraspinally, the statement that one received 5 c.c. per kilo and the other 2.5 c.c. per kilo is likely to cause a wrong impression, unless the weight of the dog is noted.

In order to study the effects of various substances when applied directly to the medulla without pressure a number of dogs were prepared by exposing the medulla, the blood-pressure and respiration being recorded as usual. The animals were placed on the abdomen with the head sharply flexed ventrally, and the medulla exposed in this position by carefully cutting a window in the occipito-atlantoid membrane. Removal of this membrane allows as a rule a small amount of cerebrospinal liquid to escape and the floor of the fourth ventricle is then easily seen. Occasionally the excision of the membrane caused a hemorrhage by wounding a vein which ran along the inner surface of this membrane. When this occurred the animal was rejected because the red corpuscles gradually settled and formed a layer over the surface of the fourth ventricle which delayed absorption. The animals were kept under ether by means of intratracheal insufflation, but the tracheal catheter was inserted through a tracheotomy wound in the neck so as to avoid an overdistention of the lungs which could be caused by a compression of the trachea due to the extreme anteflexion of the head. No experiments of this type were made on the monkey.

No aseptic precautions were taken when operating on the dog, for they were always killed painlessly before removal from the operating table by allowing a quantity of ether to enter the trachea. In the monkey, however, full strength tincture of iodine was used to disinfect the skin before operating. After completion of the experiment, the wounds were lightly wiped with the tincture and sutured with cotton ligatures which had been soaked in tincture of iodine. No bandages of any kind were used, and the wounds were never sealed with collodion. The results were excellent and pus was never seen. Most of the monkeys were used at least twice.

In one series of three monkeys the effect of intraspinal injections was studied by inspection only. The animals were held by hand and stretched

over the knee of an assistant; the hair over the lumbar spinal region was clipped, the area painted with tincture of iodine, and then the intraspinal injection was given after first obtaining cerebrospinal liquid. This method of injection is unsatisfactory because it interferes considerably with respiration, especially if the animal struggles.

From the preceding description of the procedures employed to study the effects obtained when various liquids are injected into the spinal sac, it will readily be seen that the conditions obtaining in the monkey experiments approximate much more closely to the conditions under which intraspinal injections are given in the human being, than do the experiments made on dogs. The latter animal unfortunately demands a severe operation on the spinal column before injections can be given with any certainty. In addition it hardly needs to be pointed out that the monkey is a nearer relative to man than the dog. The results obtained from the monkey are therefore *a priori* entitled to more weight than those obtained in the dog, and this inference is strengthened when it is observed that both man and the monkey seem to react in general quite similarly to intraspinal injections of sera.

Results. In general it may be said that intraspinal injections of sera with and without preservatives (0.3 per cent. tricresol, 0.3 per cent chloroform, 0.3 per cent. ether) produce qualitatively the same effect upon the medullary centres both in the monkey and the dog. The effects differ, however, quantitatively with the preservative employed, with the dosage, and with the animal species used, the monkey being strikingly more resistant than the dog. Broadly stated the respiration is first increased both in amplitude and rate for a short period of time; then, particularly in the dog, the amplitude decreases and the rate slows and the respiration may even stop for a shorter or longer period of time. The blood-pressure shows an initial rise followed by a gradual drop of varying degree. This drop is usually associated with a marked slowing of the pulse rate in the dog. The normal level is again reached after some minutes.

In the following pages a fairly detailed description of the functional disturbances caused by the intraspinal injection of the liquids mentioned will now be given, beginning with the monkey.

As far as practicable the main results will be illustrated by specimen curves of the respiration and blood-pressure, especially those which have been obtained from the monkey. In order that these tracings be as complete and comprehensive as possible, most of them will show a fifteen-minute portion of an experiment.

Experiments on Monkeys. *Tricresol Series.* In these experiments 0.3 per cent. tricresol antimeningitis serum obtained from the New York Board of Health was used. Eight monkeys were used; in four of these the intrapleural pressure (respiration) and blood-pressure were recorded; three of these four were used two times on successive days. The remaining three monkeys were held by hand, injected intraspinally with 0.3 per cent. tricresol antimeningitis serum and were then liberated and observed. These injections were repeated a number of times on the same and on succeeding days. The monkeys, as a rule, received 3 c.c. of the serum per injection, but occasionally 5 c.c. was given.

The first three monkeys, which varied in weight from 2065 to 2560 gms. were studied by inspection only, the animals being held across the knee of an assistant during an injection. No ether was administered. After each injection they were released but kept under control by means of a cord attached to the animal's belt. The injection of 0.3 per cent. tricresol antimeningitis serum were given intraspinally at rather long intervals, varying between thirty and ninety minutes in general. The animals were also reinjected on succeeding days. It developed that the injections usually produced only a moderate temporary disturbance characterized chiefly by a muscular weakness so that the animals usually were content to remain quietly in one place; associated with this was an initial slowing and deepening of the respiration followed by a more rapid and shallower respiration. None of the animals died but all were in excellent condition more than one month after the last injection when they were used for another purpose. The amounts of serum injected in one day were not great and were given as follows: Monkey 1 was a male weighing 2560 gms. On March 30 it received three times 2 c.c. and once 4 c.c. of tricresol serum. The next day it received one injection of 3 c.c. The next day (April 1) two doses of 3 c.c. each were injected. Two days later three injections of each 3 c.c. were given, and two days after this two doses of 3 c.c. each. The total amount injected was 34 c.c. in twelve doses.

Monkey 2 was a female weighing 2400 gms. On March 31 it received two intraspinal injections of 3 c.c. each; the next day one dose of 3 c.c.; two days later (April 3) two doses of 3 c.c. each, and three days later (April 6) two final injections of each 3 c.c. tricresol antimeningitis serum. The total amount was 21 c.c. given in seven injections.

Monkey 3 was a male weighing 2065 gms. and received on April 4 two

intraspinal injections of each 3 c.c. of tricresol antimeningitis serum. Two days later the same dose was repeated for the last time. This animal only received 12 c.c. in four injections.

During these 23 injections of 0.3 per cent. tricresol antimeningitis serum a collapse was observed a number of times under two apparently different conditions: (*a*) after recovery from preceding injections, the repeated insertion of the hypodermic needle, without injection of serum, caused a collapse of varying degree four times; and (*b*) after the repeated injection of tricresol serum a moderate collapse occurred two times. These effects were observed only in monkeys 1 and 2.

The third monkey exhibited no definite collapse at any time while his spinal dural sac was tapped or after receiving the injection of tricresol serum.

It is impossible to state what rôle, if any, the tricresol serum played in producing this sensitiveness to the introduction of a needle into the spinal subdural space, for no other experiments of this type with other sera were carried out. It is possible that asphyxia was a contributory factor, for the monkeys which showed a collapse always struggled vigorously when the needle was introduced; in consequence they had to be held very firmly pressed over the knee of the assistant, and this interferes considerably with respiration.

In the next series of five monkeys (4, 5, 6, 7, 8) the 0.3 per cent. tricresol serum was injected more rapidly and regularly than in the preceding series, and the animals were all etherized by the cone method. The interval between injections was either seven of fifteen minutes; in the later experiments it was usually seven minutes. No intratracheal insufflation or other artificial respiration was used as a routine measure in any of the monkey experiments. In all of these experiments except monkey 8 the blood-pressure and respiration were recorded on a smoked drum. The quantities of tricresol serum injected were large: Monkey 4, a female weighing 3455 gms., received 18 c.c. the first day and 28 c.c. the next day; it was killed later in excellent condition. Monkey 6, a male weighing 2926 gms., received 16 c.c. of 0.3 per cent. tricresol serum and the next day tolerated without trouble 18 c.c. of tricresol serum and 5 c.c. Ringer solution. This animal was also killed later in excellent condition. Monkey 7 was a female, 2865 gm., and received intraspinally in one sitting 24 c.c. of tricresol serum without any alarming effects. The next day it was in good condition, but died four days later from dysentery which it had contracted before the experiment. Monkey 8, a female of 2850 gms., was fully anesthetized with ether and then injected with tricresol serum without recording the blood-pressure or respiration. This animal received 4 doses of each 3 c.c. tricresol serum intraspinally at ten-minute intervals without any marked effect on the respiration beyond the initial deepening and slowing of the respiration usually observed during an injection. Thirty minutes after being placed

in a cage it was lively. The next day the same animal was again etherized and received 12 c.c. of 0.3 per cent. chloroform antimeningitis serum intraspinally in 3 c.c. doses with no marked effects. Nine days later the same animal again received 12 c.c. of 0.3 per cent. chloroform serum while under ether without any evil effects. Three weeks later the same animal seemed perfectly normal and was used for another purpose.

Monkey No. 5 was a female of 3225 gms. weight, and this animal succumbed after receiving only 9 c.c. of tricresol serum. This was the only death which occurred in the tricresol monkey series and the causes for its death will be considered later.

The effect which 0.3 per cent. tricresol antimeningitis serum exerts upon the blood-pressure and respiration of monkeys can best be shown by some illustrative tracings (Plates 1, 2, 3). These three sets of curves show each a period of about fifteen minutes, and were all obtained from the same animal, Monkey No. 4. Plate 1 shows the effect of the first injection upon the blood-pressure and respiration: the blood-pressure shows a strong initial temporary rise during the intraspinal injection, which is promptly followed by a drop to the 70 mm. level within four minutes after the injection. The normal level of about 100 was reattained about three minutes later. The heart beats were moderately slowed during the stage of lowered pressure. The respiration was first increased both in rate and amplitude and then the rate slowed moderately. Plate 2 shows a tracing from the same animal after it had already received 15 c.c. of 0.3 per cent. tricresol serum. The next 3 c.c. of tricresol serum, 18 c.c. in all, now produced but slight effects on the blood-pressure and respiration: the blood-pressure fell 17 mm. after the injection and recovered its original level swiftly. The heart beat was again moderately slowed. Ten minutes after this last injection, when 18 c.c. of 0.3 per cent. tricresol serum, more than 5 c.c. kilo body weight, had been incorporated, the animal was perfectly normal as far as blood-pressure and respiration were concerned. The thoracic cannula was then removed and the wound sutured, leaving a one-sided pneumothorax. The right femoral artery was ligated and the incision in the groin sutured. Within one and a half hours the monkey was moving about actively in its cage. The next day the same animal, apparently in excellent condition, was again etherized, stretched out on a table and prepared for another experiment. The respiration was recorded through the same wound in the left chest as on the day before; the blood-pressure was registered from the left femoral artery. Now the animal received five injections of 3 c.c. tricresol antimeningitis serum at fifteen-minute intervals with only slight effects on the blood-pressure and respiration. The sixth injection of 3 c.c. caused a slow, marked fall of blood-pressure from 100 mm. to 51 mm., but full recovery (98 mm.) took place within seven minutes after the injection, although this last injection was given much more rapidly than the preceding ones. The seventh dose consisted of 5 c.c. tricresol serum injected more

EXPLANATION OF FIGURES

In every tracing the large oscillations represent the respirations, and a downstroke means inspiration unless artificial respiration is given during a respiratory stoppage when the upstroke records distention of the lung.

The respiratory curve is usually cut by a straight horizontal line which represents atmospheric pressure; above the line is positive pressure; below the line is negative pressure.

The tracing above the respiratory record is the blood-pressure, obtained in the dog from the carotid artery and in the monkey from the femoral artery by means of a mercury manometer. Zero level of the pressure is recorded always by the time line.

Time is always marked in four-second intervals.

The broad white bands below the time line record the time consumed during an intraspinal injection.

In all tracings twelve-second intervals have been measured and the blood-pressure, pulse rate, and number of respirations for this interval noted in small figures on the curve. The blood-pressure readings represent the mean blood-pressure.

None of the monkeys received artificial respiration as a routine procedure.

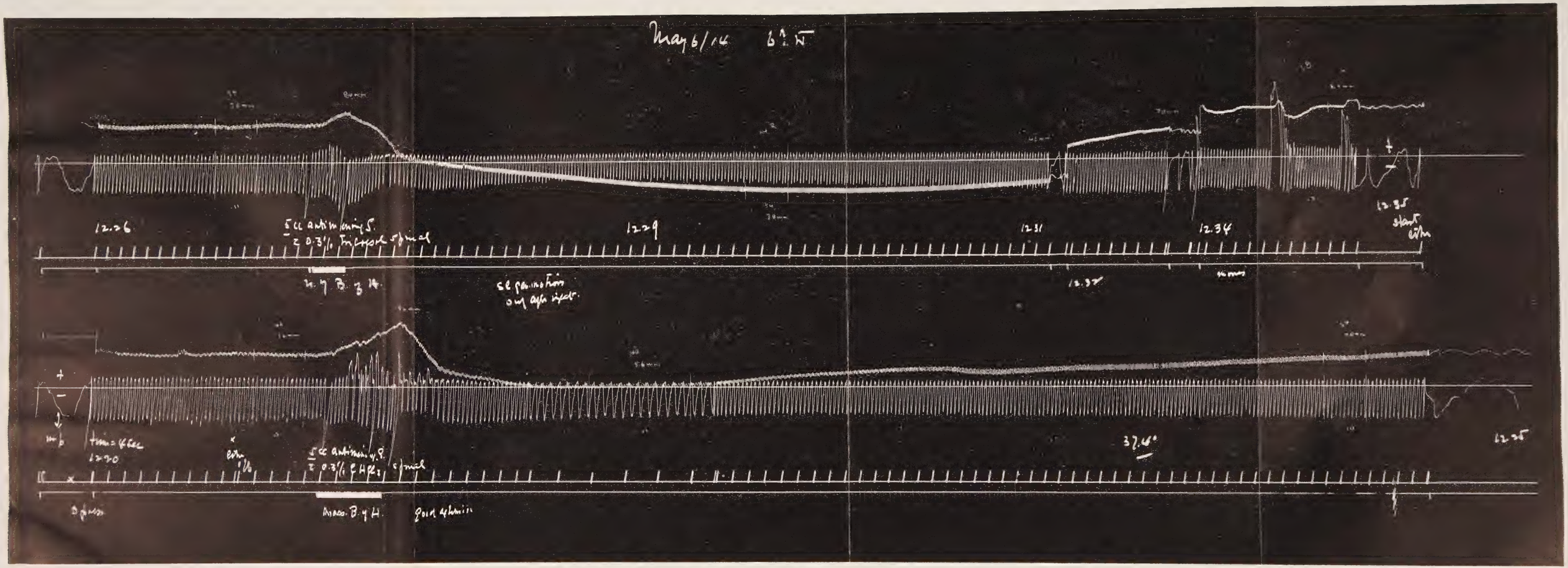
PLATE 1

Monkey No. 4, tricresol series; 3455 grams. Normal respiration. Vagi intact.

Shows the effect of 3 c.c. of 0.3 per cent. antimeningitis serum (New York Board of Health) injected intraspinally for the first time. In this monkey spinal puncture was performed while the blood-pressure and respiration were being recorded.

Note the moderate effect on the respiration, and the prompt recovery of the blood-pressure.

Compare this plate with Plate 9, which shows the profound effect of a first injection of 0.3 per cent. tricresol serum in the dog.


May 6/16
12.26
12.29
12.31
12.34
12.35
start
12.37
37.6°
12.25
min
sec

rapidly than the doses of 3 c.c. The blood-pressure dropped promptly from 94 mm. to 44 mm. but again showed swift recovery within seven to eight minutes. The respiration showed a moderate temporary decrease in amplitude and increase in rate. Plate 3 depicts this seventh injection, the animal having tolerated so far 23 c.c. of tricresol serum. The eighth injection also consisted of 5 c.c. driven in within fifteen seconds: the respiration slowed moderately at first, then accelerated markedly (from the normal rate of 65 to 100) with a moderate diminution in amplitude but never caused any apprehension. The blood-pressure, however, dropped promptly after a short initial rise from 110 mm. to 34 mm.; recovery began after about six minutes and was then accelerated needlessly by the intraspinal injection of 2 c.c. adrenalin. This injection drove the blood-pressure to 200 mm. within 1.5 minutes after the injection. Ten minutes later the respiration was 80 per minute, of good depth and the blood-pressure recorded 150 mm. The animal was apparently in excellent condition and was now anesthetized to death. This animal had therefore received in all 28 c.c. of 0.3 per cent. tricresol antimeningitis serum or 23 c.c. if we exclude the last dose because the recovery was hastened by adrenalin. This latter amount represents the enormous dose of 8 c.c. tricresol serum per kilo body weight, a dose which was borne with perfect safety. It must be remembered that the same animal received the day before 18 c.c. of tricresol serum (5.2 c.c. per kilo) and that the animal had a left-sided pneumothorax when used for the second time.

This remarkable tolerance was not an isolated instance but was also exhibited by Monkey 6 of the tricresol series. This animal was a male weighing 2926 gms. and was treated exactly as Monkey 4 just described. On the first day 15 c.c. of 0.3 per cent. tricresol serum were injected in 3 c.c. doses at fifteen-minute intervals with effects similar to those observable in Plate 1. At the end of the experiment when 5 c.c. tricresol serum per kilo body weight had been incorporated, the animal was in excellent condition. The operation wounds in the chest and right groin were wiped as usual with tincture of iodine and then sutured with cotton ligatures soaked in tincture of iodine. This animal, as a consequence of the method, also had a left-sided pneumothorax, nevertheless within one hour after being placed in the cage it seemed in excellent general condition and moved about.

The next day the same monkey was in excellent condition and was again utilized for another experiment of the same type. The pleural cannula was inserted through the same opening in the left chest which had served the day before; the blood-pressure was recorded from the left femoral artery. The monkey then received intraspinally six times at fifteen-minute intervals, 3 c.c. of 0.3 per cent. tricresol antimeningitis serum. The effect on the blood-pressure was even less than on the day before the drop not exceeding 20 mm., and the normal level was always reattained within three minutes. The respiration showed the usual alterations of rate and amplitude already

PLATE 2

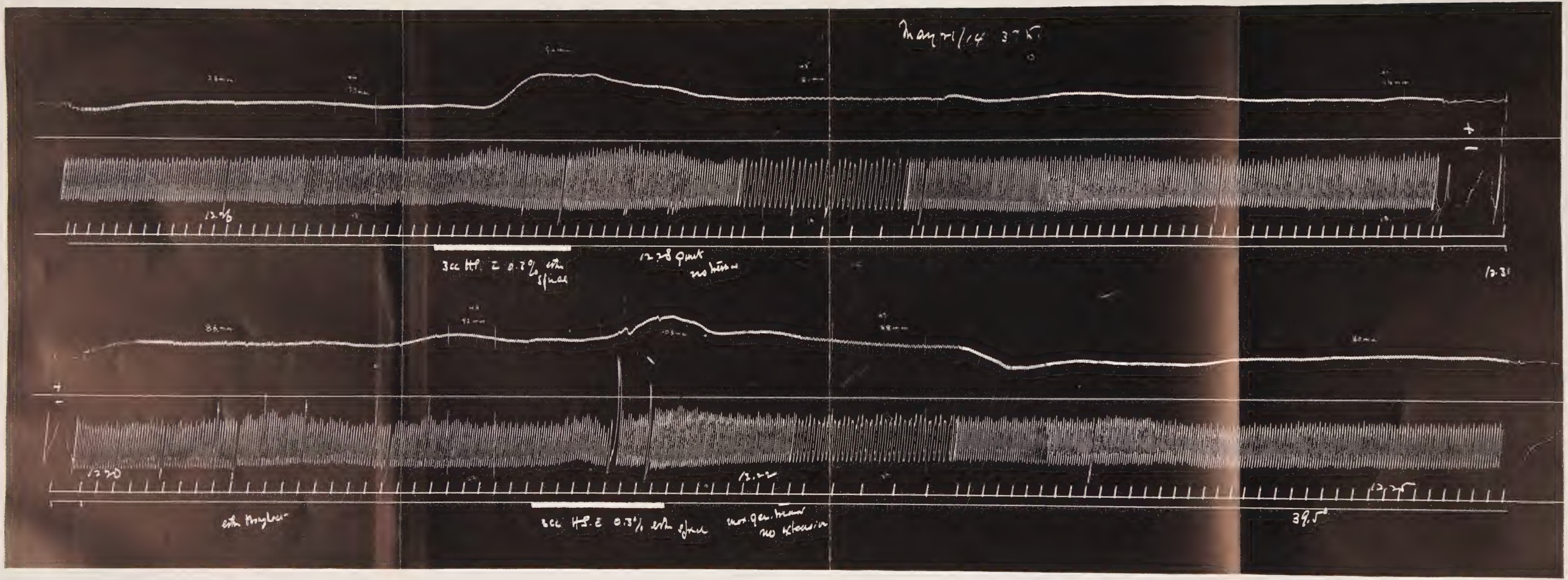
Same animal as in Plate 1; same day, later stage.

This tracing shows the effect of the sixth injection of 3 c.c. of 0.3 per cent. tricresol antimeningitis serum intraspinally.

The effect on the respiration and blood-pressure is less than that recorded after the first injection. 18 c.c. of 0.3 per cent. tricresol serum or 5.2 c.c. per kilo were thus readily tolerated.

The speed of the drum was increased periodically to facilitate counting of the respirations and pulse beats.

The wounds were now sutured, after treating them with tincture of iodine, and the animal was returned to its cage in excellent condition although it had a left pneumothorax.


3cc Hyp. E 0.3% with glucose
3cc Hyp. E 0.3% with glucose

described. During each injection, however, the animal showed convulsive general movements and gasping respirations with stoppages in active expiration, which ceased as soon as the injection was completed. There was also a slight general tremor which lasted less than a minute after the injection. After the sixth tricresol serum injection the animal was in very good condition and now 5 c.c. of Ringer solution were injected intraspinally as rapidly as possible. A tonic convulsion set in at once associated with slow, gasping respirations. These symptoms, however, swiftly grew less and after five minutes the monkey was in as good condition as before. He was then killed by ether. The animal had therefore received with safety 5 c.c. per kilo body weight of 0.3 per cent. tricresol antimeningitis serum intraspinally on one day and 6 c.c. of the same serum per kilo on the next day.

In Monkey 7 of this series the injections of tricresol antimeningitis serum were given at six to eight minute intervals instead of fifteen minutes as in other animals in order to make the test still more severe. This monkey was a female weighing 2865 gms., and was prepared for the registration of its respiration and blood-pressure in the same fashion as the other monkeys. Three c.c. of tricresol serum were injected eight times intraspinally in this animal at short intervals without producing practically anything but a temporary disturbance of the respiration and blood-pressure during and shortly after the injection. Plate 4 shows the slight effects produced by the seventh and eighth intraspinal injections of each 3 c.c. tricresol serum. In addition to the enormous dose of 8 c.c. of 0.3 per cent. tricresol per kilo animal which was tolerated without danger, 3 c.c. of 0.3 per cent. chloroform antimeningitis serum and 3 c.c. of sterile horse serum without any preservative were given intraspinally without causing any dangerous symptoms. The animal was in excellent condition at the end of the experiment, which had lasted about one hour and a half, the time consumed by the operative preparations not being counted. The wounds in the chest and groin were now sutured and the animal returned to its cage. Two hours later it was in good shape and the next day (May 8) it moved about and ate a banana. On May 11, four days after the experiment, it looked sick and fluid feces mixed with blood were found in the cage. In the afternoon of the same day the animal died. Investigation showed that the animal had a colitis, for its gut from the cecum to the rectum showed petechial hemorrhages in the mucosa with occasional erosions; the small gut was clear. No pus or excess fluid was found in the chest; the wound in the chest wall was entirely closed by a plate of fibrin. This dysentery cannot be attributed to the serum injection because this animal was taken from a group a number of which died from dysentery; its death, however, from dysentery was probably aided by the weakening effect of the operation.

In Monkey 5 of this series a number of technical difficulties were encountered. This animal was a female weighing 3225 gms. and was apparently in heat. It was so readily etherized that too much ether was given (cone

PLATE 3

Same animal as in Plates 1 and 2. Next day. Vagi intact. Left pneumothorax. The monkey was in excellent shape. It was prepared as usual for a graphic record.

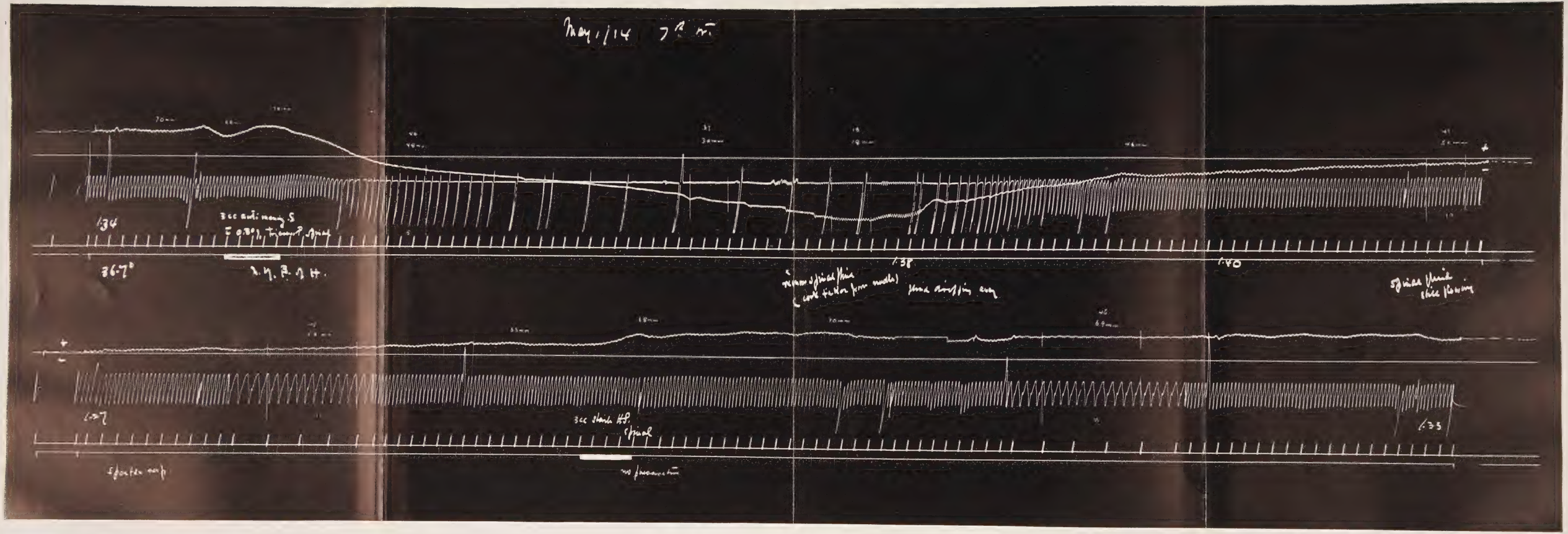
The tracing shows the effect of the seventh injection of 0.3 per cent. tricresol antimeningitis serum. The previous doses were 3 c.c. at fifteen-minute intervals, 18 c.c. in toto. The curve illustrated in the plate represents the effect of 5 c.c. injected as rapidly as the usual dose of 3 c.c.

Note the profound drop in blood-pressure from 94 mm. to 38 mm. accompanied by a slowing of the pulse from 245 to 215 per minute, while the respirations are quickened from 85 to 105 per minute with a slight reduction of the respiratory amplitude.

Prompt recovery of the blood-pressure occurred. This plate shows the harmlessness of a deep fall of blood-pressure when the respiration is normal.

Only one of the six injections preceding the one figured gave a similar drop of blood-pressure. Fifteen minutes after the seventh injection (Plate 3) another injection of 5 c.c. tricresol antimeningitis serum was given. The curve was identical practically with Plate 3; recovery of the pressure was well begun after seven minutes but was accelerated needlessly by the intraspinal injection of 2 c.c. adrenalin which raised the blood-pressure in one minute to 200 mm.

The animal was in excellent condition at the end of the experiment and had tolerated 28 c.c. of 0.3 per cent. tricresol serum, 8.2 c.c. per kilo, without any respiratory difficulty at any time.


May 1/14
1:34
36.7°
1:38
1:40
1:37
1:35

method) and respiratory recovery was slow and not complete. The placement of the pleural cannula was faulty so that registration only became possible after establishing a full left-sided pneumothorax. In addition to these mishaps, difficulty was encountered in obtaining spinal fluid. The hypodermic needle was inserted five times in three lumbar spaces before undoubted spinal fluid was obtained. Although the animal was in poor condition before any injection was given, nevertheless it tolerated two injections of each 3 c.c. of tricresol serum without any difficulty; the respiration remained fairly satisfactory and the blood-pressure, after dropping from 90 mm. to 42 mm. after the first injection, and from 94 mm. to 52 mm. after the second dose, both times regained its normal level (90 to 95 mm.) within about eight minutes after the injection. The third dose, however, produced during its injection a respiratory stoppage in active expiration lasting about ten seconds, followed by series of convulsive, deep respirations with active expiration; subsequent to this the respirations were inspiratory jerks of short duration followed by pauses in passive expiration. These respiratory attempts were about 30 to the minute, while the normal respirations had numbered 70. The blood-pressure had risen moderately during the injection and then dropped slowly to the 34 mm. level in four minutes, the respiratory jerks at that time numbering 30 per minute. The heart rate had slowed at once after the injection and four minutes later was 155, while the normal rate before injection was 220 per minute. Now, while the heart was still beating regularly, the respiration suddenly ceased entirely and the blood-pressure continued to fall. Pharyngeal insufflation was begun but did not resuscitate the animal. Unfortunately no attempt was made to withdraw some of the spinal fluid in order to decrease an important factor, that of spinal pressure. Had this been done it seems probable that the animal would have survived. Evidence for this statement will be given later (see Plate 8). Monkey No. 5 was the only monkey of the entire series of eight which succumbed to the intraspinal injection of tricresol serum.

0.3 *Per Cent. Chloroform Series.* Three experiments on two normal monkeys were carried out with 0.3 per cent. chloroform antimeningitis serum obtained from Dr. Theobald Smith. The chloroform serum was not warmed before injection. The monkeys were prepared as usual for recording the blood-pressure and respiration. Monkey No. 1 was a male weighing 2045 gms. and received at seven-minute intervals four doses of 3 c.c. each intraspinally. The effect on the blood-pressure was slight: after a short initial rise not exceeding 15 mm. the pressure declined slightly, not more than 10 mm., and within five minutes the pressure was at practically the same level as before injection. The respiration slowed slightly after the injections. Then two doses of each 3 c.c. tricresol serum were injected at seven-minute intervals which also did not affect the blood-pressure and respiration to any extent. It must be mentioned that in this experiment,

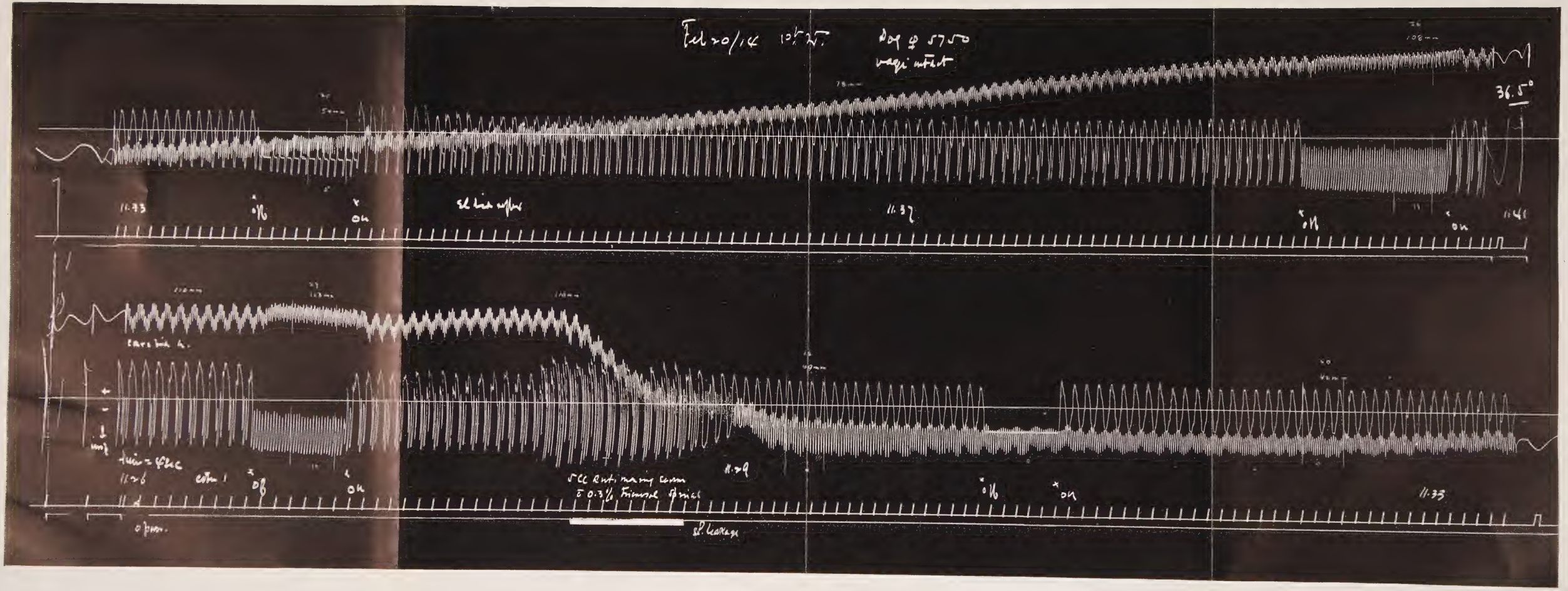
PLATE 4

Monkey No. 7, tricresol series; 2865 grams; vagi intact; normal respiration.

This tracing shows the seventh and eighth intraspinal injection of 3 c.c. of 0.3 per cent. tricresol antimeningitis serum (New York Board of Health). All of the injections were given at seven-minute intervals.

The effect on the blood-pressure was slight, beyond the short initial rise. The respiration shows an increase in rate without any marked diminution of amplitude. The initial respiratory effect of the injections (increase in amplitude with slowing and stoppage in active expiration) was largely due to the fact that the animal was not fully anesthetized.

The animal was in excellent condition at the end of the experiment after 8 c.c. of 0.3 per cent. tricresol serum per kilo, and on the next two days. Four days later it died of a dysentery contracted before the experiment.


36.5°
11.33
11.37
11.41
11.33
11.39
11.26
Carotis A.
Aut. massag. comm.
± 0.3% Frequenz Spirale
St. Leakage

the skin above the site of injection showed a slight non-hemorrhagic, boggy infiltration, as if perhaps some of the injected serum had escaped from the subdural space. This animal was killed by ether immediately after the experiment.

Monkey No. 2 of the chloroform series was a male weighing 2835 gms. and was prepared as usual for graphic registration. The animal received five injections of each 3 c.c. intraspinally at fifteen-minute intervals except the last two, which followed after seven minutes. The effect on the blood-pressure was negligible except perhaps after the third dose when the blood-pressure slowly sank 15 mm. but recovered its normal level of 90 mm. within five minutes. Now two injections of each 3 c.c. tricresol serum were given intraspinally at a seven-minute interval. These two injections hardly affected the respiration; the blood-pressure sank less than 15 mm. and the normal level was reached six minutes later. Seven minutes after the last injection of tricresol serum the respiration was 55, the blood-pressure 90. The wounds were now sutured and the monkey placed in its cage. Five hours afterward the animal ate peanuts.

On the next day the same animal, in excellent general condition, was again etherized and prepared for registration. The experiment lasted over two hours and during this time the animal received at seven-minute intervals (except the second which followed the first injection after fifteen minutes) 23 c.c. chloroform serum, 21 c.c. tricresol serum, and 10 c.c. Ringer solution. After this enormous dose the monkey was in good condition, its blood-pressure was 77 mm., its respiration 65, and its heart beats numbered 180 to the minute. In order to be perfectly certain that the injection had really been subdural, 10 c.c. of a warm gelatine solution colored with methylene blue was injected through the needle tapping the subdural space (the needle had remained *in situ* throughout the experiment). Even after this injection the animal was still alive and had to be killed by giving an excess of ether. Autopsy showed, contrary to expectation, that the dural spinal sac was not distended with fluid. After slitting the dura and exposing the brain, the sensory and motor nerve roots were found a deep blue; the surface of the cerebellum and cerebrum showed a lighter blue. No blue color was observed in the lateral ventricles or the fourth ventricles, though these areas were left exposed to the air for some hours. There can therefore be no doubt that the tremendous quantity of liquid injected during the experiment had all entered the spinal subdural space.

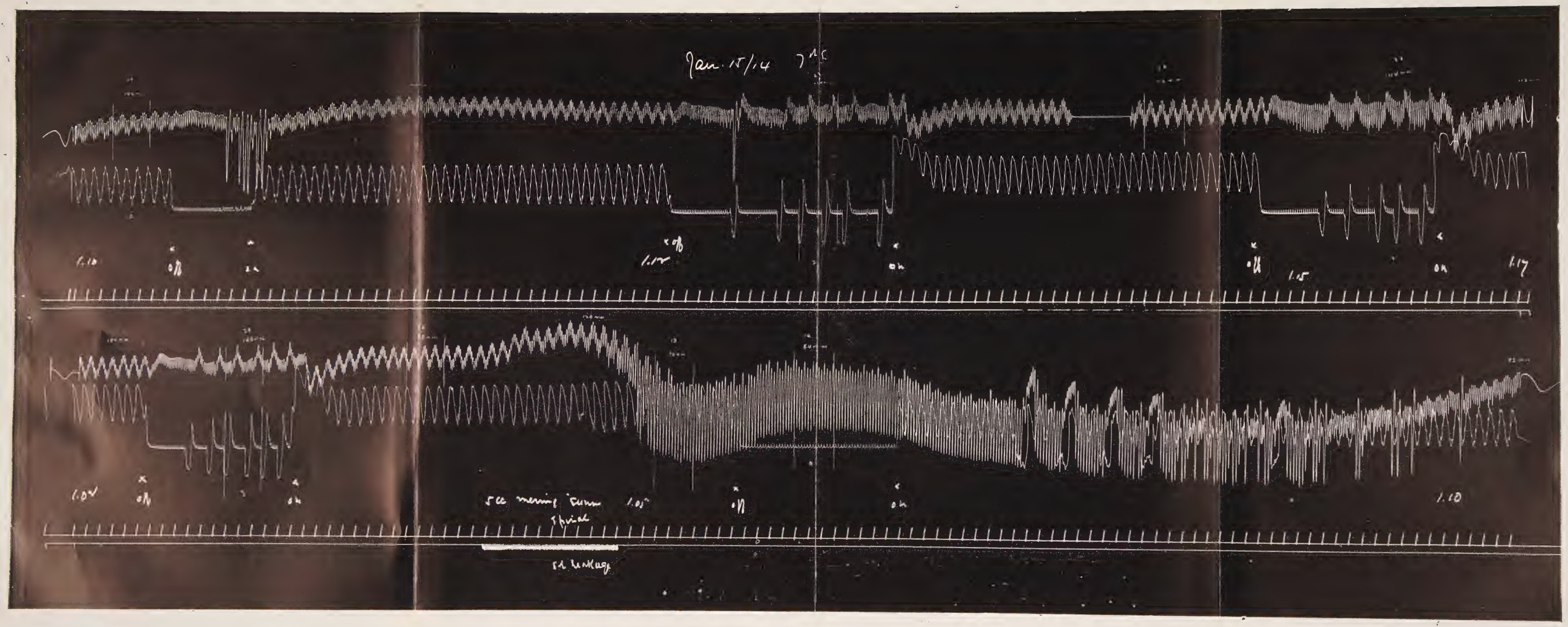
The effect produced by a series of injections of chloroform serum in Monkey 2 used for the second time were similar to those already recorded: practically none on the respiration, the amplitude diminished very slightly for some minutes after the injection with occasionally a slight slowing of the rate; the blood-pressure showed a moderate, gradual drop which only once exceeded 20 mm. (see Plate 5), and the level before injection was always attained within six minutes after the injection. Plate 5 will illustrate this

PLATE 5

Monkey No. 2, chloroform series; 2835 grams; vagi intact; normal respiration; left pneumothorax.

This monkey had received intraspinally on the day before (May 5) 15 c.c. of 0.3 per cent. chloroform antimeningitis serum (Massachusetts Board of Health); 6 c.c. of 0.3 per cent. tricresol antimeningitis serum and its blood-pressure and respiration had been recorded. The intervals between the injection had varied between seven and fifteen minutes. After the experiment it was sutured and returned in excellent condition to its cage, although it had a left pneumothorax.

On the next day (May 6) it was again prepared for recording while in excellent condition. Plate 5 shows the slight effect exerted by two intraspinal injections of each 3 c.c. of 0.3 per cent. chloroform antimeningitis serum, after the animal had already tolerated 3 c.c. of 0.3 per cent. tricresol serum and 9 c.c. of 0.3 per cent. chloroform serum. The preceding chloroform serum injections produced about the same effect as those pictured in Plate 5.


Jan. 15/14 7 AC
1.10
1.17
1.05
1.10
1.10
5 cc mercury
Thyroid
5 cc Lenhartz

clearly; these two curves were obtained after the animal had already received 15 c.c. of chloroform serum and 6 c.c. of tricresol serum. Plate 6, obtained from the same animal after it had received 18 c.c. of chloroform serum and 6 c.c. of tricresol serum, shows clearly the difference between the effects of tricresol and chloroform antimeningitis serum, although the drop in blood-pressure with the chloroform serum is greater than that usually observed. The chloroform serum caused a drop of 16 mm. in the blood-pressure followed by a prompt steady recovery of its former level; the tricresol serum brought on a profound drop of 38 mm. followed by a slightly slower recovery. The respiration after the chloroform serum was only slightly affected, and that in the direction of a slowing, with only a slight change in the amplitude; after the tricresol serum the respiration shows a definite temporary decrease in its amplitude with an increased rate which tended to persist for some time.

These experiments on Monkey 2, weighing less than 3 kilos, demonstrate strikingly what enormous doses of serum with chloroform and tricresol as preservatives can be tolerated intraspinally without danger: on one day the monkey received 15 c.c. of chloroform serum and 6 c.c. of tricresol serum; on the next day the same animal readily tolerated 21 c.c. of chloroform serum, 23 c.c. of tricresol serum and 10 c.c. of Ringer solution (see Plates 5 and 6).

Ether Serum Series. Two experiments were made in two monkeys with 0.3 per cent. ether horse serum. Monkey 1 was a male weighing 2965 gms. and was prepared as usual for recording. It received 12 c.c. of ether serum in 3 c.c. doses at seven-minute intervals. The injections not only caused no fall of blood-pressure but the initial rise of blood-pressure which follows all intraspinal injections in the monkey was maintained for some minutes, more or less, and then the pressure reached practically the same level as before the injection. The respiration in this animal exhibited rhythmical fluctuations in amplitude, but no marked changes in rate. It must be stated that this animal received too much ether during the operative procedures and its general condition was not satisfactory when the injections were begun. Moreover, a full pneumothorax had to be established on the left side in order to obtain records of the respiration. Nevertheless, the monkey was in good condition at the end of the experiment after it had received more than 4 c.c. per kilo of ether-serum. After suturing the wounds in the left pleura and groin, the monkey was placed in a cage and within one hour moved about actively. Recovery was complete, and twenty-four days later it weighed 200 gm. more than on the day of experiment, and was then used for another purpose.

Monkey 2 of this series was a male weighing 3575 gms. and was prepared as usual for records. It received six injections of each 3 c.c. ether serum at seven-minute intervals, a dose of more than 5 c.c. per kilo body weight. The blood-pressure, as in Monkey 1 showed no fall but the same tendency

PLATE 6

Same animal as in Plate 5, later in the experiment, after the monkey had already received 18 c.c. of 0.3 per cent. chloroform serum and 6 c.c. of 0.3 per cent. tricresol serum (3 c.c. doses, usually at seven-minute intervals).

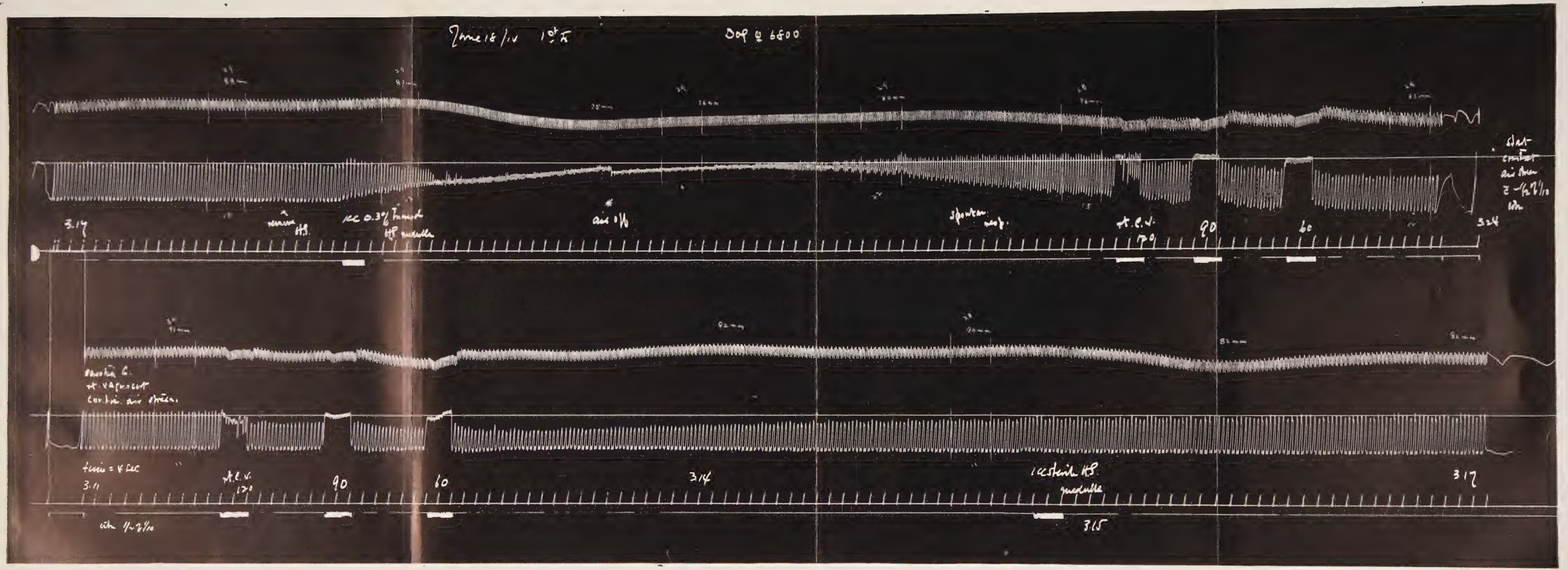
The plate records the effect exerted by 5 c.c. of chloroform serum driven in rapidly intraspinally. Only a moderate effect on the blood-pressure and respiration was produced.

Seven minutes later 5 c.c. of 0.3 per cent. tricresol serum were driven in swiftly. With tricresol serum the blood-pressure drop was considerable, but recovery was complete in seven minutes. The respiration was increased in rate and slightly diminished in amplitude after the tricresol injection.

This curve as well as Plate 3 show well that a low blood-pressure after 0.3 per cent. tricresol serum is not dangerous as long as the respiration is not impaired.

This monkey received a number of other injections and tolerated in all 21 c.c. of 0.3 per cent. tricresol antimeningitis serum, 23 c.c. of 0.3 per cent. chloroform antimeningitis serum and 10 c.c. Ringer solution and was in excellent condition at the end of the experiment when the animal was killed.

Gelatine, colored with methylene blue, injected intraspinally in this monkey at the end of the experiment furnished the proof on autopsy that all the injections had really entered the dural sac.


Temoin 15 l/s 10ème
DDP à 6800
3.14
Arrêt HP.
ACC 0.3% Tirage HP medulla
Air 1/8
Spontané arrêt.
T.C.V.
90
60
3.24
Start contact air thorax 2 - 1/2 1/10 sec.
Narcose C.
T. C.V. fréquent
Contin. air thorax.
Accès = 4 sec
3.11
T.C.V. 120
90
60
3.14
Accès tussif. HP medulla
3.17
3.15
sec 1/2 1/10

to maintain for some time the initial rise of pressure caused by the injection. Several minutes after the injection the pressure reached usually the original level before injection and did not fall below it. No marked alterations occurred in the respiration either in rate or amplitude, except that the respiration became somewhat deeper after 4 c.c. had been injected. The curves of Plate 7 show the effects described very well; they were obtained after the monkey had already received 12 c.c. of ether-serum.

While suturing the pleural wound, leaving a full left pneumothorax, the respirations became shallow, gasping, and the face grew gray. The ether was discontinued at once and the suture of the chest hastily completed. Although the respiration improved a little, it was considered best to give pharyngeal insufflation[1] for a few minutes. The color of the tongue swiftly became pink and the spontaneous respirations grew deeper and more frequent. After five minutes the pharyngeal insufflation was discontinued and the animal now breathed well spontaneously. It was placed in a cage and two hours later moved about quite actively. Eight days later it appeared in good general condition although the skin wounds had opened, and it had a slight cough. Twenty-five days after the operation it was found dead and autopsy showed a right-sided pneumonia. There was no pus in the left chest where the pleural cannula had been inserted, but the left lung was largely atelectatic. The cord looked normal, there were no adhesions or signs of inflammation. It is hardly necessary to state that this death cannot be attributed to the intraspinal injections.

Sterile Horse Serum Series. In these experiments a sterile horse serum without any preservative was employed. The serum was several months old. Two experiments were made in two days on one monkey. This animal weighed 3295 gms., and was a male. After the usual preparation 15 c.c. of sterile horse serum and 3 c.c. of tricresol serum were injected intraspinally in 3 c.c. doses at fifteen-minute intervals. The sterile horse serum caused hardly any alteration in the blood-pressure or respiration, beyond the ordinary initial effect during and slightly after the injection. The injection of 3 c.c. tricresol serum, however, caused a prompt drop of about 30 mm of mercury but recovery was practically complete after ten minutes. The respiration this time was slowed by the tricresol serum from 80 per minute to 60 per minute. Twelve minutes after this last injection the animal was in a satisfactory state: his blood-pressure was 76 mm., the heart rate 180, and the respirations were 65 per minute. Suture of the wounds was completed without any mishap and the animal removed to its cage where it sat up at once. During the next three days it was in excellent condition and on the third day it was again prepared for an experiment. Four injections of each 3 c.c. sterile horse serum were injected intraspinally at fifteen-minute intervals without practically affecting the blood-pressure

[1] S. J. Meltzer, Jour. Amer. Med. Assoc., 1913, lx, 1407.

PLATE 7

Monkey 2, ether series; 3575 grams; vagi intact; normal respiration.

This animal had already received 12 c.c. of 0.3 ether horse serum intraspinally (3 c.c. doses, at seven-minute intervals). Note the absence of any decided drop in blood-pressure during the next two injections recorded in Plate 7, but that the blood-pressure tends to remain raised for a period of time. The effect on the respiration is very slight.

and respiration. The fifth injection was 3 c.c. of tricresol serum given fifteen minutes later. Now the blood-pressure dropped promptly from 98 mm. to 54 mm. the pulse rate remaining at 225 to 230, while the respiration slowed from 100 to 70 per minute; the amplitude remaining the same. After fifteen minutes full recovery of the original blood-pressure, pulse rate and respiratory rate had occurred. Now 3 c.c. sterile horse serum without any preservative was injected with the usual practical absence of any effect on the blood-pressure and respiration. Twelve minutes after this injection another dose of 3 c.c. tricresol antimeningitis serum was injected intraspinally: the blood pressure rose slightly (10 mm.) and then dropped within two minutes to the 20 mm. level; the respiration after the initial quickening slowed to 20 per minute (original rate 95) and were feeble; occasionally deeper gasps occurred. As this condition did not improve, pharyngeal insufflation was begun two minutes after the injection, and a short time later the spinal fluid was allowed to escape by removing the cork in the needle cap. The blood-pressure gradually improved and the respiration became stronger. Ten minutes after the beginning of pharyngeal insufflation it was discontinued: spontaneous respiration was now of excellent depth and numbered 40 to the minute; the blood-pressure was 46 mm. at this time; seven minutes later it reached 63 mm. and the respirations were 55 per minute. Now 3 c.c. of sterile horse serum without any preservative were injected intraspinally: the blood-pressure rose to 69 mm. and remained at that level; the respiration was not altered in rate, but the amplitude became very slightly less. Five minutes later 3 c.c. of 0.3 per cent. tricresol antimeningitis serum was injected with the same result as the other tricresol serum injection: the blood-pressure showed the usual initial rise and then dropped slowly within the next three minutes to the 18 mm. level; the pulse rate sank from 230 to 185 and then to 90 (cardiac block), the respiration after a short quickening slowed from 55 per minute to 4 per minute and were gasping in character. Now the intraspinal pressure was reduced by removing the cork in the hypodermic needle and clear fluid began to drip away rapidly. No artificial respiration of any kind was given. In about thirty seconds the blood-pressure began to rise, the respirations became quicker and three minutes later were 50 per minute, while the blood-pressure was 52 mm. and the heart rate 235. Six minutes after this, or twelve minutes after the tricresol serum injection, the blood-pressure was 72 mm., the heart rate 245 and the respirations 55. The animal was now in good condition and was later anesthetized to death. It is regrettable that no attempt was made to suture the animal in order to permit it to survive. Plate 8, reproduces the striking and instructive picture which the animal furnished during the last injection with tricresol serum.

Experiments on Dogs. The experimental results which were obtained in the dog when this animal was injected intraspinally with

PLATE 8

Monkey No. 1, normal serum series; 3295 grams; vagi intact; normal respiration; left pneumothorax for three days.

This animal had been used for a graphic experiment April 28, and had then received intraspinally in 3 c.c. doses at fifteen-minute intervals 15 c.c. sterile horse serum and 3 c.c. of 0.3 per cent. tricresol antimeningitis serum, and was in good shape at the end of the experiment when the animal was sutured and returned to its cage with a left-sided pneumothorax.

On May 1, four days later, the same animal was in excellent condition and was again used for a graphic record. Previous to the injections noted on Plate 8, the monkey had already received in 3 c.c. doses at seven- to fifteen-minute intervals 15 c.c. of sterile plain horse serum and 6 c.c. of 0.3 tricresol antimeningitis serum. The sterile horse serum produced practically no effect on the blood-pressure and respiration.

The tracings on Plate 8 show the slight effect exerted by 3 c.c. of sterile plain horse serum upon the respiration and blood-pressure, but the succeeding injection of 3 c.c. of 0.3 per cent. tricresol antimeningitis serum caused first a slight short stimulation of the respiration and then a marked slowing and deepening of the respiration with stoppages in passive expiration. The blood-pressure fell promptly, after a short initial rise, from 70 mm. to 18 mm. and the cardiac rate slowed from 230 to 80. At this point when the condition seemed hopeless, the stopper was removed from the cap of the hypodermic needle which tapped the spinal dural sac, and fluid dripped away, rapidly at first, then more slowly. Within thirty seconds the blood-pressure and respiration began to improve rapidly and a few minutes later the animal was in good condition. After fifteen minutes the blood-pressure was 74 mm., the respiration 60, and the pulse rate 230 per minute.

This tracing shows very well the striking beneficial results of merely reducing the intraspinal pressure after accidents of this type.

plain serum or with serum containing preservatives, were quantitatively markedly different from those observed in the monkey. The dog, under the experimental conditions previously described, showed itself much more sensitive to these injections than the monkey.

In all the dogs except in the medulla series, laminectomy was performed and the respiration and blood-pressure recorded. Before describing the results obtained in the dog it must again be stated that all the dogs of the various series were anesthetized by means of intratracheal insufflation and it will be remembered that this method at the same time furnishes an efficient artificial respiration. It is this method which explains the discrepancy between the results to be recorded and those obtained for example by Hale.[1]

Tricresol Series. Six dogs were used for the intraspinal injection of 0.3 per cent. tricresol serum and their weights ranged between 4250 and 6600 gm. The doses injected varied between 3 and 6 c.c. per kilo[2] animal, except in one instance, Dog No. 1, where more than 11 c.c. per kilo were given. Only one Dog, No. 4, succumbed after an injection, and this animal, which had already tolerated 6 c.c. per kilo, probably also would have survived if the final injection of 5 c.c. had not been given while the animal was breathing spontaneously; moreover, insufflation was not begun in the attempt to resuscitate the animal until respiration had ceased for three minutes and was only continued for a few minutes. At the conclusion of all the experiments all the dogs were breathing spontaneously when insufflation was stopped and the blood-pressure of the six animals[3] varied between 80 and 138 mm. of mercury, the heart rate between 135 and 200, and the spontaneous respiration between 5 and 70 per minute.

The first injection of tricresol serum caused in all animals a deep drop in blood-pressure which began usually before the injection was finished; this drop was occasionally preceded by a short slight rise. The level reached during this drop was often 45 mm., and was always associated with a marked slowing of the pulse rate and an increased amplitude of the pulse beat, unless the vagi had been cut or atropin had been given. The pressure and heart rate gradually increased after the injection and within ten minutes the former level was usually reattained. The respiration was quickened and deepened during an injection, then rapidly slowed and usually stopped in an expiratory position for a length of time which varied between a fraction of a minute and several minutes, when recovery quickly set in. Plate 9 illustrates exceptionally severe effects both upon the blood-pressure and

[1] Loc. cit.

[2] These doses are not absolutely correct, because in dogs a certain variable leakage always occurred after several injections had been given intraspinally.

[3] In dog 4 the blood-pressure was 76 mm., the spontaneous respiration 5 to 10, and the heart rate 140 per minute before the final injection was given.

PLATE 9

Dog No. 6, tricresol series; 5750 grams; vagi intact; intratracheal insufflation throughout except when marked "off." This tracing shows an exceptionally severe reaction to 5 c.c. of 0.3 per cent. tricresol antimeningitis serum injected intraspinally for the first time. The respiration showed an initial short stimulation of both rate and amplitude during the injection, and then the respiration stopped in passive expiration for about four minutes (see section where the insufflation is discontinued marked "off—on"). The large oscillations recorded during this time are due to the mechanical remissions in the volume of the air stream. The blood-pressure began to fall before the injection was finished and reached the 42 mm. level, the pulse rate dropping at the same time from 135 to 80 per minute (vagus centre stimulation). Recovery of both respiration and blood-pressure was prompt and practically normal nine minutes after the injection.

This dog tolerated 15 c.c. more of tricresol serum and was in excellent condition at the end of the experiment.

respiration after a first injection; it also shows well how complete the recovery may be after comparatively few minutes. This dog showed a drop in blood-pressure from 110 mm. to 42 mm. after 5 c.c. of 0.3 per cent. tricresol antimeningitis serum, the heart rate fell from 135 to 80 per minute, and the respiration was entirely abolished for about four minutes. Recovery was prompt and twelve minutes after the injection the blood-pressure, heart rate and spontaneous respirations were identical with those obtained before the injection.

Subsequent injections of tricresol serum in the dogs did not often cause more severe blood-pressure depression than the first, but recovery at times became slower when 4 to 5 c.c. per kilo animal were exceeded. A similar effect was observed with the respiration. After 5 c.c. and more per kilo had been injected the spontaneous respirations at times reappeared more slowly and were slow and deep with inspiratory stoppages, the rate being 5 to 10 per minute; the blood-pressure in this stage, however, was never lower than 80 mm. When the amount did not exceed 4 c.c. per kilo the spontaneous respirations after recovery ranged between 35 and 70 per minute at the end of an experiment, and the blood-pressure varied between 80 and 100 mm.

Plate 10 shows the respiratory slowing brought on by large doses of 0.3 per cent. tricresol serum. This dog No. 1, had received 30 c.c. of tricresol serum before the injection which the curve illustrates. The next 5 c.c. of tricresol serum, which brought the total amount to about 7 c.c. per kilo dog, produced only a moderate fall of blood-pressure (from 98 to 70 mm.) in spite of a powerful slowing of the pulse rate (from 140 to 65) due to stimulation of the vagus centre. After about five minutes the effects of this vagus centre stimulation had largely disappeared and the blood-pressure recorded 140 mm. and the heart rate 105. The respiration which was slow before this last injection (15 per minute) was slightly stimulated at first by the injection,[1] and then stopped for less than three minutes when a group of respirations with long inspiratory stoppages appeared; two minutes later spontaneous respirations were about 10 to the minute. This slowing of the respiration was not always permanent; in this same animal, for example, the next two injections of tricresol serum were followed by a much prompter and more complete respiratory recovery than Plate 10 illustrates.

The readiness and completeness with which a dog may recover from a severe effect of tricresol serum on the blood-pressure and respiration is well shown by Dog 2. This animal was a female, weighing 4250 gms. and almost died from asphyxia after the first injection of 5 c.c. of 0.3 per cent. tricresol serum, because a plugged tracheal tube had been employed through some error. Nevertheless after the insertion of a new tracheal tube another injection of 5 c.c. tricresol serum was given fifteen minutes after the first one, at a time when complete recovery from the asphyxia had not yet set

[1] This stimulating effect was much more pronounced in subsequent injections of tricresol serum in the same dog.

PLATE 10

Dog No. 1, tricresol series; 4750 grams; vagi intact; intratracheal insufflation air-ether throughout except when marked "off—on."

This dog had already received 30 c.c. of 0.3 per cent. tricresol serum before the injection recorded on this tracing. The blood-pressure was excellent, 100 mm., but the spontaneous respirations were slow, 15 per minute, and showed inspiratory stoppages with active expirations (stimulation of inspiration and expiration).

The injection of 5 c.c. of 0.3 per cent. antimeningitis serum now given stimulated the respiration but slightly and then caused stoppage of the respiration in passive expiration (inhibition of the respiratory centre). This inhibition was a little later broken by a series of five respirations each showing a stoppage in the inspiratory position lasting about four seconds (stimulation of inspiration); now an inhibition of all respiration again follows, but seven minutes after the injection spontaneous respirations of the same type as before the injection appear (respirations with inspiratory pauses and active expiration.)

The blood-pressure rose during the injection of the serum from 98 to 120 mm. and then dropped to 70 mm. while the pulse rate fell from 140 to 65 per minute (vagus centre stimulation). In spite of this tremendous slowing of the pulse rate the blood-pressure began to rise for a time (stimulation of both vagus centre and vaso-constrictor centre). For some time on the blood-pressure now escaped occasionally from the vagus stimulation, especially during the group of respirations with long inspiratory pauses. Seven minutes after the injection, respiration, blood-pressure, and pulse rate were practically as before the injection.

Subsequent injections of 0.3 per cent. tricresol serum showed the combined stimulation of vagus and vaso-constrictor centres still more markedly.

in. During the injection the pressure sank gradually and the heart slowed; this slowing rapidly increased so that less than thirty seconds after the end of the injection no heart beats were visible on the curve and the blood-pressure fell to about 6 mm. The respiration was entirely abolished by the injection. Ether was now discontinued but insufflation was kept up and the foot of the board elevated; the air pressure in the tracheal system was also slightly increased. The heart beats reappeared less than two minutes after the injection and the blood-pressure began to rise slowly. No spontaneous respirations were, however, observed until eleven minutes had elapsed; the blood-pressure at this time was 40 mm. This dog nevertheless received two more spinal injections at fifteen-minute intervals, and thirteen minutes after the last injection or about forty-five minutes after the time when no heart beats were visible on the curve, the blood-pressure was 80 mm., the heart rate 140, and spontaneous respirations 35.

Chloroform Series. Four dogs were used in this series; their weights were 9000, 4200, 4250, and 8000 gms. The serum injected was 0.3 per cent. chloroform antimeningitis serum obtained from the Massachusetts Board of Health, and the quantity used varied from 25 to 35 c.c. As usual, the dose was 5 c.c. for each injection. None of the dogs succumbed to the injection.

The effects on the blood-pressure and respiration were definitely less severe after most of the injections than that exerted by tricresol serum; the fall of blood-pressure was less and the respiratory stoppage was of shorter duration. Nevertheless in each dog except No. 2 a profound drop of blood-pressure occurred which in one instance reached 70 mm. (from 123 to 54 mm.) in two minutes after the injection. These profound blood-pressure drops usually were only observed as a result of the first injection, the succeeding injections caused only moderate depressions. Recovery resulted in most instances within ten minutes; in the example mentioned above where the blood-pressure fell 70 mm., recovery began at once after the low level was reached and seven minutes later was 112 mm.

The respiration showed the same type of effect noted in the tricresol series. After the initial increase in rate and amplitude during the injection, the respiration slowed and stopped for a period of time ranging from a few seconds to several minutes, the length of the stoppages increasing at times with the number of injections. In only one dog, No. 2, did the animal fail to reëstablish an efficient spontaneous respiration. This animal weighed about half as much as the other dogs in this series, 4200 gms., and received in all 30 c.c. of chloroform serum. The first injection of chloroform serum gave a profound drop in blood-pressure, described above, and stopped the respiration for four minutes. The next three injections of each 5 c.c. stopped the respiration for not longer than two minutes. The fifth injection was given while the animal was breathing spontaneously and insufflation was only begun after the respiration had stopped entirely for 1.5 minutes and when the blood-pressure was 36 mm. Fifteen minutes after this last injec-

PLATE 11

Dog No. 8, medulla series; 6800 grams; right vagus cut; left intact; continuous air stream (no remissions); downstroke = inspiration; rt. c.v. = central stump of the right vagus. The numbers indicate the coil distance in millimeters of a Petzold inductorium driven by two Daniell cells. In this dog the medulla only was exposed.

The lower tracing shows the effect of applying 1 c.c. of sterile, plain horse serum to the floor of the fourth ventricle; the blood-pressure drops slightly for a short time, but the spontaneous respiration shows no effect.

Now 1 c.c. of 0.3 per cent. tricresol serum was applied to the medulla after first removing the plain serum. The respiration first showed an increase of rate accompanied by a decrease in amplitude which swiftly led to a stoppage of the respiration in passive expiration. Then the insufflation of air was stopped, but nevertheless spontaneous respirations began about one minute later, at first rapid and of small amplitude, but swiftly the amplitude increased and the rate decreased until the rate was 60 per minute and the amplitude practically normal. The tricresol serum had not been removed, it must be noted.

The blood-pressure showed only a slight drop with no change in the pulse rate during the experiment.

Stimulation of the central stump of the right vagus caused the same effect upon the respiratory centre before and after the application of tricresol serum. The stimulations caused no strong effect upon the vasomotor centres at any time, although the after-effects of the stimuli were slightly more pronounced after the application of the tricresol serum than before (vasomotor centre more irritable after the tricresol than before).

Compare this tracing with Plates 9 and 10, when the tricresol serum was injected intraspinally.

tion, although the blood-pressure and respiration had not yet fully recovered a sixth injection was administered. The blood-pressure dropped from 70 mm. to 36 mm. and the respiration ceased entirely and did not return during the next hour. The blood-pressure was raised by a number of adrenalin injections, but spontaneous respiration did not reappear.

The other three dogs showed at the end of the experiment a blood-pressure which varied from 82 to 142 mm., pulse beats from 130 to 230 and spontaneous respiration of good amplitude from 25 to 50 per minute.

Ether Series. This group consisted of four experiments. The dogs weighed 8750, 9200, 8500, and 5850 gms., and all received from 20 to 25 c.c. of horse serum to which 0.3 to 0.4 per cent. ether by volume had been added. The serum was not warmed before injection. None of the dogs succumbed.

The effect of the blood-pressure and respiration was in general much less than that exerted by either the chloroform form or tricresol serum. The drop in blood-pressure was slight to moderate, usually associated with a slowing of the pulse rate (vagus pulses) unless the vagi were cut; recovery was very swift and a normal level was reattained after a minute or two. In many instances the drop in blood-pressure in spite of a strong slowing was quite slight. The respiration was also only slightly affected after the large majority of the injections and the respiratory stoppages when they occurred did not last longer than a fraction of a minute.

A serious effect was obtained only once and this occurred in Dog 1, a female of 8750 gm. Both vagi were cut in this animal before any injections were given, and the respirations were in consequence slower than normal. The first two injections of each 5 c.c. of 0.3 per cent. ether serum separated from each other by a fifteen-minute interval, caused practically no effect on the respiration or blood-pressure. Now the intratracheal insufflation was discontinued and the animal was allowed to breathe spontaneously. Then the third injection was given intraspinally. The respiration first slowed strongly and then stopped entirely before the injection was finished. The blood-pressure after an initial rise dropped abruptly from 128 mm. to 38 mm. within forty-five seconds after the end of the injection. Before this low level was quite reached spontaneous respiration began again, after a stoppage in expiration of about forty-five seconds; both the respiration and blood-pressure rapidly became better, but after four minutes the respiration again slowed and now showed long inspiratory stoppages. At this point intratracheal insufflation was reëstablished and ether was discontinued. After eight minutes conditions were worse, the blood-pressure was lower and the respirations slower. Now 1 c.c. of adrenalin in 3 c.c. of Ringer solution was injected intraspinally. The blood-pressure and respirations improved at once, and eleven minutes later the blood-pressure registered 108 mm., the pulse beats were 265, and the respirations were 25.

One hour after this injection which produced such a deep effect, two more injections of ether serum were given. These two injections separated

by fifteen minutes, caused only slight effects on the blood-pressure and respiration. At the end of the experiment the animal had a blood-pressure of 86 mm., pulse of 220, and his respiration numbered 35 per minute.

Horse Serum Series. In this series sterile horse serum without any preservative was injected intraspinally. Five experiments were made, but in three of these either tricresol or chloroform serum was injected first before plain serum was used. Because these later injections produced well-marked effects on the blood-pressure and respiration, these combination experiments were rejected because the results could not definitely be attributed to the plain horse serum.

In two experiments nothing but sterile horse serum, at least a month old and without any preservative, was injected intraspinally. The dogs weighed 5250 and 6000 gms. and both were males. The first dog received 30 c.c. and the second one 35 c.c. sterile serum intraspinally and both were in good condition at the end of the experiment. Dog 1 (vagi intact) at that time had a blood-pressure of 80 mm., pulse rate of 165, and 15 respirations per minute. Dog 2 (vagi cut) registered a pressure of 76 mm., a pulse rate of 175, and a respiration of 55 per minute.

Every injection in Dog 1, whose vagi were intact, caused a drop in blood-pressure varying from 20 to 50 mm., and the pulse was at the same time increased in amplitude and slowed in rate (vagus pulses). The drop was usually preceded by a short moderate rise of pressure. The drop usually lasted as long as the slowing of the pulse was marked, but four times out of the six injections in this dog the original level was reattained at a time when the pulse rate was still 15 to 40 beats slower than normal. The duration of the drop varied from a fraction of a minute to four minutes.

In Dog 2, where the vagi were cut, the injection of plain horse serum produced a drop of blood-pressure which usually did not exceed 15 mm. This drop established itself more slowly and in addition was preceded by a more sustained rise than in Dog 1 (vagi intact). During the low blood-pressure level the rate was usually slowed 10 to 20 beats although the vagi were sectioned in this animal. The duration of the drop was usually less than one minute.

One severe drop of blood-pressure was obtained in Dog 2: the seventh injection of 5 c.c. plain serum with no preservative was given twenty minutes after the sixth dose, while the animal was breathing spontaneously; before the injection was completed the blood-pressure fell from 106 mm. to 64 mm. in less than one minute and three minutes later reached the 50 mm. level, the pulse slowing from 175 to 165. Then recovery set in without any insufflation or other aid and twelve minutes after the lowest level was reached (seventeen minutes after the injection) the blood-pressure recorded 92 mm. The respiration throughout this time was spontaneous and showed no marked alterations of any kind. It should be added that the next injection which was given seven minutes after the last one produced only the ordinary effect.

The respiration in Dog 1 (vagi intact) showed the usual initial quickening and deepening of the respiration during the injection, followed by a slowing with inspiratory prolongation and a stoppage of respiration in the expiratory position which lasted from a half minute to two minutes. The respirations were at first slow but the normal rate and depth was usually reattained quickly. In Dog 2 (vagi cut) inspiratory stoppage of the respiration was the most pronounced phenomenon during the injection, and the following respiratory stoppage in expiration did not exceed one minute in duration.

Both dogs received plain horse serum intraspinally while breathing spontaneously and the effect was apparently no more severe in all, except one instance, than when given during artificial respiration. This single and striking exception occurred in Dog 2 and has already been described.

Ringer Solution Series. Two male dogs weighing 7500, 7000 were used and both received nine injections of 5 c.c. Ringer solution intraspinally. The vagi of both were intact. The injections were given at seven-minute intervals, sometimes even more rapidly. The affect on the blood-pressure and respiration were in general similar to those described for the ether or plain horse serum series: initial rise of the blood-pressure followed by a slowing of the pulse rate and a moderate drop of pressure which usually did not exceed 20 mm. Within one minute the normal level and pulse rate was reattained. The respiration often was merely slowed, and when stoppage in expiration took place, this stoppage never lasted longer than one minute.

Both animals were in good condition at the end of the experiment and each tolerated two injections of 5 c.c. tricresol antimeningitis serum with considerably less effect on the blood-pressure and respiration than tricresol serum usually produced: the blood-pressure sank about 20 mm. with a moderate slowing of the rate, and recovered its level within a few minutes. The respiration was not stopped at all in any of the four tricresol injections. Ten minutes after the last injection both dogs showed blood-pressure 110, 108 mm., pulse rate 195, 175, and respiration 30, 55 respectively.

Formalin Experiments. A few experiments in dogs only were made with a serum to which formalin in the proportion of 1 or 2 per 1000 serum had been added. With 1 to 1000 the effect on the blood-pressure and respiration was considerably less severe than with 0.3 per cent. tricresol. This investigation was not continued because formalin is a powerful protein coagulant and there is at present no evidence available that the antimeningitis serum is not injured by this preservative.

Local Applications of Tricresol Solutions to the Medulla. This series of experiments was carried out in order to observe the effect of 0.3 per cent. tricresol when applied directly to the fourth ventricle. A procedure of this kind reduces the factor of pressure of the tricresol solution so that it can be neglected, and the effects observed may safely be attributed to the tricresol solution itself.

Ten experiments were carried out in dogs. In the first four experiments 0.3 per cent. tricresol in 0.9 per cent. salt solution was employed. This solution was applied to the medulla at about five-minute intervals while the animal was breathing spontaneously or during intratracheal insufflation. In none of these four tests did the saline tricresol solution cause a marked lowering of the blood-pressure or a stoppage of the respiration. When ether was pushed so that the spontaneous respiration began to fail and the blood-pressure fell, then the tricresol saline hastened the disappearance of respiration. If now the tricresol application were regularly continued, but the ether stopped while air insufflation was maintained for about five minutes longer before this also was discontinued, then nevertheless spontaneous respirations began almost at once, and the blood-pressure continued its ascent which began as soon as the ether was stopped.

The last six experiments of this series were made by applying 0.3 per cent. tricresol horse serum to the medulla. Before each application the cerebrospinal liquid was cautiously removed with absorbent cotton and replaced by 0.6 to 1 c.c. of the tricresol serum. The blood-pressure and respiration were recorded as usual. In five of these six dogs one vagus was cut in the neck and the central stump used for stimulation of the medullary centres. Five of these dogs weighed between 6 and 10 kilos, only one weighed less (Dog 5).

Four of these six experiments showed that several applications of 0.3 per cent. tricresol serum in seven- to ten-minute intervals produced only slight alterations of the blood-pressure and respirations; the respirations usually became more rapid and of smaller amplitude; the blood-pressure sank about 10 mm.; both respiration and blood-pressure became practically normal within a few minutes. At the end of these four experiments a molecular solution of $MgSO_4$ was applied to the medulla; in each dog the respiration slowed and stopped permanently, the blood-pressure fell gradually and the animal died without a struggle.

In two experiments, Dogs 6 and 8, the medullary application of 0.3 per cent. tricresol serum caused a respiratory stoppage. In Dog 6 two applications of each 0.6 c.c. tricresol serum caused first a short increase in the rate coupled with a diminished amplitude of the respirations, then the rate slowed and respirations ceased for less than a minute when they again appeared, although the tricresol solution had not been removed. Removal of the tricresol solution and the application of Ringer solution hastened the recovery. The blood-pressure was not affected at all. In this experiment the intratracheal insufflation was continued throughout.

In Dog No. 8, two applications of each 1 c.c. of 0.3 per cent. tricresol serum to the medulla caused a stoppage of the respiration in the expiratory position after a short period or respiratory stimulation of the rate, as in Dog No. 6. During this stoppage the intratracheal insufflation was discontinued one minute after the practical abolition of respiration, but nevertheless spontaneous respirations began one minute later and rapidly became normal

in amplitude, though faster in rate. It must be noted that the tricresol solution was not removed but was allowed to remain in contact with the medulla. The blood-pressure showed a drop of 13 mm. Ten minutes after the first application, the solution was removed and replaced by another cubic centimeter of tricresol serum. The blood-pressure was at this time 92 mm., the pulse rate 150, and the respiration numbered 60 per minute. The application again caused a stoppage of spontaneous respirations which lasted about two minutes when spontaneous respirations appeared (the insufflation of air was stopped thirty seconds after the beginning of respiratory stoppage). The blood-pressure in this instance dropped slowly from 88 to 79 mm. Seven minutes after the application the blood-pressure was 100 mm., the pulse 165, and the spontaneous respirations 70 per minute. In this test the tricresol serum was again allowed to remain in contact with the medulla throughout and again complete recovery resulted, without aiding the animal in any way. Plate 11 shows the effect produced by the first application of tricresol serum on the medulla of Dog 8 of this series. The local application of 0.3 per cent. tricresol solution thus produces quite different results from the intraspinal injection of the same liquid.

Discussion. From the description of experiments given in the preceding pages a number of facts appear with clearness. It has been shown in the tricresol series that monkeys tolerate the intraspinal injection of 0.3 per cent. tricresol serum very well, even when previously subjected to an operation which interferes to some extent with respiration (partial pneumothorax). Out of eight monkeys only one succumbed and this one died after receiving about 3 c.c. per kilo body weight. The reasons for this death will be considered later. The other monkeys survived the injections in an excellent fashion, though the doses given were often considerably greater than the one which caused the single death of this series. Indeed the quantities tolerated under unfavorable conditions by the monkeys were a source of surprise. Among the operated monkeys of this series (pleural cannula, spontaneous respiration, cannula in the femoral artery, ether anesthesia throughout) two monkeys were used on successive days for the same experiment, the injections on the second day being given while the animal had a full one-sided pneumothorax. Monkey 4 received 18 c.c. of 0.3 per cent. tricresol serum intraspinally (5.2 c.c. per kilo) in six injections at fifteen-minute intervals, and was in excellent condition at the end of the experiment. On the next day the same animal, in apparently excellent shape, was again injected with 23 c.c. of 0.3 per cent. tricresol serum (8.2 c.c. per kilo) with full recovery.

Plates 1 and 2 show the effects of the first and sixth injection on the first day; and Plate 3 shows the result of the seventh injection, this last time 5 c.c., on the next day. The intervals were again fifteen minutes. Similar results were obtained with Monkey 6 which was operated in the same fashion as Monkey 4. Monkey 6 received on the first day 15 c.c. of tricresol antimeningitis serum in five injections at fifteen-minute intervals and was in excellent condition at the end. The wounds were than treated with tincture of iodine and sutured as usual. No attempt was made to remove the pneumothorax which resulted on removal of the pleural cannula. On the next day the animal seemed in very good condition and was again prepared for a graphic record of the respiration and blood-pressure. On this day it received intraspinally in 3 c.c. doses at fifteen-minute intervals 18 c.c. of tricresol antimeningitis serum (6 c.c. per kilo) without any alarming symptoms. Then 5 c.c. of Ringer solution were driven in as fast as possible, but the animal recovered within a few minutes. Another monkey, number 7, received 21 c.c. of tricresol antimeningitis serum intraspinally (8 c.c. per kilo) in 3 c.c. doses at seven-minute intervals and was in excellent condition at the end of the experiment and on the next day, in spite of a one-sided pneumothorax. Four days after the injection, however, the animal died of dysentery which it had contracted before the injection, for five of its normal mates died of the same disease.

These experiments show decisively that large quantities of 0.3 per cent. tricresol antimeningitis serum are tolerated very well by monkeys who have been subjected to severe operations. But these experiments may be considered acute and it might be suggested that the result would be different if the injections had been repeated a number of times on different days and the animals then observed for a period of days. Experiments of this type were therefore also carried out. Monkeys 1, 2, and 3 received intraspinal injections of 2 to 3 c.c. of 0.3 per cent. tricresol antimeningitis serum per kilo on different days without any anesthesia, and were then kept under observation for at least one month. All of them were alive and in excellent condition after that period. Monkey 1 was injected on five different days, Monkey 2 on four, and Monkey 3 on two days. Only one of these monkeys showed an alarming collapse after an

injection, but recovered promptly after a period of pharyngeal insufflation.[1] These experiments show that repeated injections of fairly large amounts of 0.3 per cent. tricresol serum do not cause undesirable effects which appear only after some days.

It must be emphasized that all the monkeys received intraspinal injections without any artificial respiratory aid.

In the tricresol dog series similar results were obtained. Out of the 6 dogs which received from 3 to 6 c.c. of 0.3 per cent. tricresol serum per kilo body weight, one dog succumbed after having tolerated 6 c.c. per kilo. This dog died after the next injection of 5 c.c., apparently because this last injection was given without intratracheal insufflation while the animal was breathing spontaneously. If this last injection had also been given during intratracheal insufflation it seems probable that the animal would have survived like his companions.

These results in dogs are at variance with those observed by Hale[2] who obtained a fatal issue when "somewhat larger" doses than 2 c.c. per kilo were injected intraspinally. This difference is entirely due to the different methods which Hale employed, for in his experiments the dogs were allowed to breathe spontaneously, while in my experiments almost invariably intratracheal insufflation was used which prevents asphyxia due to any temporary functional failure of the respiratory centre.

Sources of Danger from 0.3 per cent. Tricresol Serum. One of the main dangers in the employment of 0.3 tricresol serum seems to be the increased intraspinal pressure. This is indicated quite clearly in a number of experiments both in the dog and in the monkey. Indeed, in the monkey the death producing factor may be largely the increased intraspinal pressure. In the monkey, for example, the injection of a few cubic centimeters of tricresol serum after the previous intraspinal incorporation of plain horse serum without any preservative may produce a stoppage of the respiration broken occasionally by short gasps, a profound drop in blood-pressure, and a marked slowing of the pulse. Nevertheless the mere removal of spinal fluid may suffice to restore blood-pressure,

[1] Collapse after the mere introduction of a hypodermic needle into the spinal dural sac was also observed in this series, and has already been described. It is possible that a preceding partial asphyxia due to the method of holding these lively animals, is partly responsible for the collapse.

[2] Loc. cit., p. 14.

respiration, and pulse to normal within a few minutes. An experiment of this type is beautifully shown in Plate 8.[1]

In this animal a similar serious effect in the respiration and blood-pressure had been obtained before on the same day, and the monkey had rallied with similar speed after some spinal fluid was withdrawn though this time he was also aided by pharyngeal insufflation. This respiratory aid was probably not necessary, for the second respiratory failure yielded promptly when merely spinal fluid was withdrawn as shown in Plate 8.

The single death of the tricresol monkey series, animal number 5, gave a tracing of the respiration and blood-pressure after the fatal injection which is very similar to those figured on Plate 8. In this fatal case pharyngeal insufflation was administered, but no spinal fluid was withdrawn. It seems probable that the issue would have been different had some spinal fluid been allowed to escape.

In the dog also, pressure plays a considerable role. This is shown by the differences in effect between intraspinal injections of tricresol serum and its local application to the medulla. In this animal species the intraspinal injection of 0.3 per cent. tricresol usually causes a powerful drop in blood-pressure, associated with a marked slowing of the pulse and a more or less marked abolition of respiration (see Plates 9 and 10). But the local application of the same tricresol solution on the medulla of the dog only exceptionally (in two dogs out of ten) produces a pronounced stoppage of the respiration (see Plate 11) and never, in my experience, a strong, continued drop of blood-pressure with a slowing of the pulse. Here again the only difference seems to be one of pressure; there is practically none when the tricresol solution is applied locally, but when an injection is given intraspinally there must be a rise of intraspinal pressure until the injected liquid is absorbed.

It is possible that the condition of the medullary centres previous to the injection of tricresol serum is of importance. Monkey 5 of the tricresol series, for example, had been almost killed by an excess of ether during the operation and the experiment was carried out before it had recovered completely. This animal succumbed after receiving only 9 c.c. of 0.3 per cent. tricresol serum intraspinally.

[1] The blood-pressure reached its normal level a few minutes later on the tracing following the one printed in Plate 8.

The symptoms were practically identical with those observed in another monkey, used for the second time, when large doses of serum both normal and tricresol, had been injected. In this latter monkey it will be remembered that the symptoms were promptly abolished by the mere withdrawal of some spinal fluid.

These experiments show that the stress laid by Flexner on the role of increased intraspinal pressure in the production of death in human beings after tricresol meningitis serum is experimentally well founded.

Although increased intraspinal pressure apparently suffices to explain largely the causation of dangerous symptoms in monkey, and the differences observed in dog when tricresol serum is applied locally to the medulla or injected intraspinally, nevertheless there is evidence that the tricresol itself exerts an effect. This is indicated by the stronger blood-pressure effect obtained in monkeys after tricresol serum than after chloroform, ether, or plain horse serum. In the dog also the same difference between the various sera is observed, tricresol serum usually causing a more profound blood-pressure drop than the other sera. In addition the dog, but not the monkey, usually exhibits a severer interference with the respiration after tricresol serum than after plain serum. Moreover, as mentioned previously, the mere local application of 0.3 per cent. tricresol serum on the medulla of the dog may occasionally produce a transient stoppage of the respiration. All these facts indicate that 0.3 per cent. tricresol does affect the medullary centres, but the action is definitely much more pronounced in the dog than in the monkey. The nature of these medullary effects will be discussed in a following section.

Another source of danger, which was observed only in unanesthetized monkeys, is the production of a collapse by the mere introduction of the needle into the subarachnoidean space of the spinal cord. This collapse is usually marked by a slowing and weakening of the respiration, which may be so great that artificial respiration (pharyngeal insufflation) is necessary to save the animal. These effects were obtained four times in two monkeys of the three in this series, and occurred after the animal had already tolerated some injections of tricresol serum. The collapse could not be obtained at will, and these and the remaining animal gave no alarming reactions

when the spinal dural sac was punctured repeatedly in order to bring on a collapse. It seems probable that a preceding partial asphyxia is an important factor in producing this type of collapse. The two monkeys which showed it struggled violently while being held across the knee of the assistant. In order to immobilize them sufficiently to permit an intraspinal insertion of the needle, the chest and abdomen had to be pressed firmly across the knee, and this must have interfered with respiration. In addition to this, the asphyxia may have led to an increased intraspinal pressure, for Dixon and Halliburton[1] have demonstrated that asphyxia, however produced, always leads to a considerable increase in the secretion of the cerebrospinal liquid.

Analysis of the Effect of Increased Intraspinal Pressure and Tricresol on the Medullary Centres. The chief danger which results to the organism when the intraspinal pressure is raised by tricresol serum is an interference with efficient respiration due to an action upon the respiratory centres. This action was not great in most of the monkey experiments and large quantities of 0.3 per cent. tricresol serum injected intraspinally by syringe produced usually but slight effects on the respiration (see Plates 2, 3, and 4). Nevertheless a serious stoppage may be obtained now and then as shown in Plate 8 where the respiration practically ceased until the intraspinal pressure was reduced. In dogs, however, temporary cessation of respiration is a fairly constant accompaniment of most intraspinal injections of 0.3 per cent. tricresol serum, and this abolition of respiration often lasted some minutes, even though intratracheal insufflation was maintained throughout the period of cessation of spontaneous respiration. The respiratory centre of the dog is thus much more sensitive to 0.3 per cent. tricresol serum than that of the monkey. The same fact is indicated by the ease with which respiratory stoppages are obtained in the dog after the injection of sera with and without preservatives or even by Ringer solution alone. In the monkey, on the other hand, no marked respiratory effects are usually obtained with any serum beyond those which occur when the injection is driven in rapidly (compare Plates 4 and 7) especially when the animal is not completely under anesthesia.

[1] Jour. of Physiol., 1913, xlvii, 334.

This respiratory failure in the dog after tricresol injections has been interpreted by Hale[1] as a paralysis of the respiratory centre due to tricresol, although he admits that increased intracerebral pressure plays some rôle. It has already been shown that increased intraspinal pressure plays a very important rôle in the causation of serious symptoms both in the monkey and dog and it must now be determined whether all the available facts support Hale's assumption that the respiratory centre is really paralyzed in the dog after large doses of tricresol serum.

The analysis of the effects observed after the intraspinal injection of tricresol serum or any fluid, is made difficult by the fact that the functional alterations observed are or may be the resultant of antagonistic actions upon the medullary centres. Thus a stimulation, either inhibitory or excitatory, of both the vagus and vasomotor centres must neutralize one another to some extent, though both centres may be clearly recognized at work in the blood-pressure curve in some instances (see Plate 10); or the respiratory centre may show both stimulation of inspiration as well as a stimulation of inhibition of inspiration. On the other hand, however, it can easily be determined whether or not a centre has been paralyzed, for the function presided over by that centre must then disappear permanently, or at least the recovery must be very slow. It will be shown in the following that the changes produced by 0.3 per cent. tricresol serum injected intraspinally can readily be explained as the result of central stimulation, either excitatory or inhibitory, and that a paralysis can be excluded.

When 5 c.c. of 0.3 per cent. tricresol serum is injected into the spinal dural sac of the dog for the first time, the usual effect is a respiratory stoppage in passive expiration which persists for a variable length of time. The recovery is usually complete within a few minutes. Here obviously a paralysis of the respiratory centre cannot be assumed, the recovery is too prompt (see Plate 9). Moreover, after large doses of 0.3 per cent. tricresol serum, so large that with Hale's method the dog would surely succumb, for example with 6 c.c. per kilo, the respirations are still good and each may show an inspiratory tetanus (see Plate 10), which of course means a stimulation of inspiration. If another injection of tri-

[1] Worth Hale, loc. cit., pp. 14, 18.

cresol serum is then given intraspinally the respirations stop now in passive expiration for a variable number of minutes (inhibition of inspiration), and then respirations of the same inspiratory type as before the injection appear (see Plate 10). The stoppage in expiration must therefore be interpreted, it seems to me, as an inhibition of the respiratory centre and not as a paralysis. This supposition is strengthened by observations which show that an intraspinal injection, given while an animal shows shallow, slow respirations due to preceding tricresol injections, nevertheless brings out a short series of rapid respirations of large amplitude. Here again the facts speak definitely for inhibition and stimulation of the respiratory centre and not for a paralysis, as it is obviously impossible for a paralyzed structure to send out a series of strong normal impulses.

This distinction between an inhibition and an intoxication or paralysis of a structure is not academic, in spite of the fact that the results of both may be disastrous to an animal. If a centre is merely inhibited no damage to the structure itself is necessarily implied, there is merely a stoppage of function, the cells themselves being intact; they will function as soon as the inhibition wears off sufficiently, and the organism will survive if tided over the critical period. If, however, a centre is paralyzed, this means a damage to that centre and recovery can only take place after this damage has at least partly been repaired, which is necessarily a slow process. If, therefore, a vital centre is inhibited there is the probability that the centre will again resume its activity if given sufficient time, and if its function is in the meantime replaced. When the centre inhibited is the respiratory centre this is very easily and readily done by instituting adequate artificial respiration. It is for this reason that the tricresol dog series reported in this paper showed such excellent results after the injection of large doses of tricresol serum; all the dogs were injected while intratracheal insufflation was maintained except in one dog, number 4, 4750 grams, which succumbed after having tolerated 30 c.c. of 0.3 per cent. tricresol serum, apparently because the last injection was given while the animal was breathing spontaneously.

The stimulation of excitatory and inhibitory functions by 0.3 per cent. tricresol serum is not limited to the respiratory centre of the dog, it is also clearly exhibited by the vague and vasomotor

centres of the medulla. Almost any injection of 5 c.c. of 0.3 per cent. tricresol serum in the dog brings on a definite slowing of the pulse rate which is often very pronounced for some time. The pulse rate, for example, may drop from 135 to 80 per minute, or from 140 to 65 (see Plates 9 and 10). This means undoubtedly that the vagus centre has been stimulated by the tricresol serum, for section of the vagi or atropin abolishes this great slowing of the pulse. The vasomotor centre also of the dog exhibits reactions which are most readily explained by a stimulation or inhibition. The first injection of tricresol serum in a dog usually causes a drop in blood-pressure, and this drop may be profound; it may fall from 110 mm. to 42 mm. (see Plate 9). This drop, however, can only be partly explained as a result of vagus centre stimulation, for a drop will still occur if the vagi have been sectioned. The tricresol serum, therefore, must have exerted an effect on the vasomotor centre, and this effect may either have been an inhibition of the normal vasomotor tonus or a stimulation of the vasodilating centre. An intoxication or paralysis can be excluded by the swift recovery which occurred within twelve minutes in an unusually severe example (see Plate 9). Moreover the behavior of the centre during subsequent injections of tricresol serum shows quite clearly that intoxication and paralysis can be excluded. After several injections of 0.3 per cent. tricresol serum a stage may be reached where the stimulation of the vagus centre produced by an injection becomes very pronounced and where, in spite of the considerable slowing of the pulse rate, the blood-pressure nevertheless rises so that it may greatly exceed the normal level. Here evidently both the vagus and the vaso-constrictor centres are stimulated at the same time. Such a combined stimulation of vagus and vaso-constrictor centres is shown in Plate 10. This tracing was obtained from a dog of 8750 grams which had already received 6 c.c. of 0.3 per cent. tricresol serum per kilo before the injection was given which the curve illustrates. From these data it is therefore permissible to conclude that the vasomotor centre also is not intoxicated or paralyzed but is, on the contrary, stimulated by large doses of 0.3 per cent. tricresol serum. Attention may be called here to a statement of Hale[1] that the "blood-pressure always

[1] Loc. cit., p. 17, italicized in the original.

falls" after the intraspinal injection of tricresol serum in the dog. This I have found by no means always true in my experiments. Plate 10, for example, shows only a moderate drop of the mean blood-pressure, and in subsequent injections of tricresol serum in the same animal I have obtained tremendous rises in blood-pressure with stoppage of the respiration in expiration quite comparable to Hale's figure[1] illustrating a fatal rise of intraspinal pressure after the injection of plain serum without any preservative. This tracing of Hale shows very well a stoppage of respiration in the expiratory position and a stimulation of both the vagus and vasomotor centres resulting in a strong rise of blood-pressure although the pulse slows from 300 to 192 per minute. I have obtained similar results after large doses of 0.3 per cent. tricresol serum, with this difference that the tricresol dog survived.

From the behavior of the respiratory, vagus and vasomotor centres of the dog after large doses of 0.3 per cent. tricresol serum have been injected intraspinally, the inference may thus justly be drawn that the effects observed are the results of a stimulation either excitatory or inhibitory of these centres. These effects, however, may be disastrous to the dog for they interfere with an efficient respiration, and the combination of cessation of respiration together with a low blood-pressure will be fatal to the dog sooner or later because a vicious circle is formed, unless artificial respiration is maintained for some time after each injection.

A low blood-pressure in itself after 0.3 per cent. tricresol serum does not seem to be dangerous to the life of the animal provided that respiration is maintained either spontaneously or artificially. This has been observed both in the monkey and the dog. Plate 10 shows a prompt recovery of the blood-pressure after a drop of 71 mm. of mercury; in Dog 2 of the same series the blood-pressure fell abruptly to practically zero after 19 c.c. of 0.3 per cent. tricresol serum intraspinally, and the curve showed no heart beats. Nevertheless intratracheal insufflation was maintained and the animal not only recovered but tolerated two further injections of each 5 c.c. tricresol serum. Twelve minutes after the last injection its blood-pressure was 80 mm., its pulse rate 140, and its spontaneous respirations 35 per minute.

[1] Loc. cit., p. 13.

In the monkey also low blood-pressure after tricresol serum does not seem to threaten life. For example, Plate 3 shows a drop from 94 mm. to 43 mm. after the intraspinal injection of 5 c.c. of 0.3 per cent. tricresol serum. Recovery took place within ten minutes without any aid. The respiration was not much affected beyond a transitory quickening of the rate and a slight diminution of the amplitude of each respiration.[1]

Another marked drop of blood-pressure in the monkey is recorded in Plate 6 after 5 c.c. of 0.3 per cent. tricresol serum. This animal had already received 18 c.c. of 0.3 per cent. chloroform serum and 6 c.c. of tricresol serum. The dose now injected caused a drop from 76 mm. to 38 mm; spontaneous recovery resulted within six minutes. The respirations in this animal also were quickened and slightly reduced in amplitude but never showed any signs of failing. The most severe blood-pressure drop in the monkey is shown in Plate 8. In this animal the respiration failed and the blood-pressure dropped to the 18 mm. level. Nevertheless prompt recovery, both of blood-pressure and respiration, resulted as soon as the intraspinal pressure was reduced by allowing the spinal fluid to escape through the hypodermic needle.

These results concerning the comparative harmlessness of considerable drops of blood-pressure both in the dog and monkey after intraspinal injection of tricresol serum, unless associated with respiratory failure of some degree, do not invalidate the observation of Sophian[2] that the blood-pressure drop is an accurate guide in judging what quantity of serum can safely be injected intraspinally in the human being. Every danger signal in the human subject must be observed during a therapeutic intervention, and as the blood-pressure has shown itself a good index in the hands of Sophian, it should always be used when serum is injected intraspinally in the human being. It is, of course, self-evident, even without the work reported in this paper, that the respiration also should be watched just as carefully as the blood-pressure, and injection should be discontinued temporarily as soon as the respiration shows alterations.

[1] This monkey, it must be pointed out, had already received 18 c.c. of 0.3 per cent. tricresol before the 5 c.c. which the plate shows; moreover the same animal had been used the day before for the same type of experiment and had then tolerated easily 18 c.c. of 0.3 per cent. tricresol intraspinally. The monkey weighed 3453 grams.

[2] Jour. Amer. Med. Assoc., 1912, lviii, 843.

Comparison of Sera Employed. From the description already given of the effects exerted by the various sera used in this investigation it is seen that they can be arranged in order of their effect on the blood-pressure and respiration. In the dog the greatest action on the blood-pressure and respiration was exerted by 0.3 per cent. tricresol serum; 0.3 per cent. chloroform serum produces also a well-marked blood-pressure drop and stoppage of the respiration, but the severity of these changes is almost always much less than with 0.3 per cent. tricresol serum; the difference is especially outspoken in the effect on the respiration, the stoppages being almost always less than those obtained with 0.3 per cent. tricresol serum. The action of 0.3 per cent. ether serum is still less than that of the chloroform serum, and the respiration and blood-pressure are usually only moderately affected. Plain horse serum perhaps is somewhat less active in its effect on the blood-pressure and respiration than the ether serum though the difference is not pronounced.

None of the sera tested in the dog were without some adverse effect, both on the respiration and the blood-pressure. Plain horse serum caused at times respiratory stoppages in passive expiration which lasted longer than a minute, and in one instance after an injection of 3.5 c.c. plain serum while the dog (vagi cut) was breathing without any aid, a prompt, profound drop of blood-pressure from 106 mm. to 50 mm. occurred while the rate merely slowed from 175 to 165, the respiration remaining unaltered at 45 per minute. Full recovery took place within twenty minutes. This effect was probably due to an inhibition of the tonus of the vasomotor centre, and was quite similar to the drop of blood-pressure obtained after 0.3 per cent. tricresol serum.

In the monkey the same gradation of the sera holds in general except that the effects of all are strongly less than those observed in the dog. 0.3 per cent. tricresol serum, for example, only exceptionally produces a marked effect on the respiration even after large doses have been injected intraspinally (see Plates 2, 3, 4), and no marked respiratory effects were observed at all after chloroform, ether, and plain serum. The difference between the sera is best emphasized in the monkey by the behavior of the blood-pressure. 0.3 per cent. tricresol serum causes usually a more or less pronounced drop of blood-pressure (see Plates 1, 2, 3, 4); 0.3 per

cent. chloroform serum has much less effect (Plates 5, 6); 0.3 per cent. ether serum causes no drop of blood-pressure at all but raises the pressure for a short period of time (see Plate 7); and plain horse serum also practically does not affect the blood-pressure, the rise being less than with ether serum.

These experiments show that ether and chloroform sera are better than 0.3 per cent. tricresol if we consider the blood-pressure and respiration as criteria. Moreover, they have this great advantage that they can be largely, if not entirely, removed by warming the serum container before injection. The preservative thus may fulfill its function as long as it is considered desirable. It may be added that the antimeningitis serum of the Massachusetts Board of Health is preserved by 0.3 per cent. chloroform due to the initiative of Dr. Theobald Smith. The suggestion to try ether serum I owe to Dr. Simon Flexner and this serum, as already stated, is superior to chloroform serum in the physiological test.

Effect on the Spinal Cord. The spinal cord was usually examined both in dogs and monkeys after an experiment. In the dog the bloodvessels of the cord were usually found moderately injected after 0.3 per cent. tricresol serum, especially in the lumbar and lower thoracic region. At times the cord at the site of injection showed some maceration of the surface, but only in one instance were hemorrhages found in the substance of the cord itself, and these hemorrhages were limited to the lumbar region. Similar vascular injections of the pia-arachnoid vessels were observed after the employment of the other sera, but the injection was usually less. Superficial macerations of the cord were also observed in these series.

In the monkey the cord was examined shortly after an experiment or after an interval of days or weeks. No damage of the cord was ever seen, and the injection of the bloodvessels was never pronounced even after 0.3 per cent. tricresol serum. In no instance were adhesions noted between the cord and dura, nor did the cord show signs of infection in spite of the fact that the antisepsis practiced during an intraspinal injection was far from perfect.

It was interesting to note that even after very large doses of serum the monkey's spinal dural sac did not contain a large amount of fluid even when the autopsy was performed less than thirty minutes after the last injection. Absorption of the serum seems to be rapid, and this fact explains the rapidity with which the blood clotted in the arterial cannula and adjoining section of artery during blood-pressure experiments.

Effect of Preservatives on the Opsonins of the Antimeningitis Serum. This series of experiments was kindly carried out by Dr. Martha Wollstein. The results show that 0.3 per cent. tricresol, 0.3 per cent. chloroform, and 0.3

per cent. ether affect the opsonin content about equally when tested after one week, one month or three months. The meningococcus strain used was the same which the New York Board of Health employs for this purpose.

SUMMARY. 1. The monkey (macacus rhesus) usually tolerates readily the repeated intraspinal injection of large doses of 0.3 per cent. tricresol antimeningitis serum. The spontaneous respiration is generally not disturbed.

2. Doses of 0.3 per cent. tricresol antimeningitis serum as large as 8 c.c. per kilo were injected intraspinally with subsequent recovery, even when the monkey had a partial pneumothorax.

3. Dangerous alterations of the respiration and blood-pressure in the monkey after 0.3 per cent. tricresol antimeningitis serum given by syringe are apparently largely due to increased intraspinal pressure, for the mere reduction of this pressure has sufficed to bring about a prompt recovery.

4. The medullary centres of the monkeys (vagus, respiratory, and vasomotor) are very resistant to the action of sera when injected intraspinally, strikingly more so than those of the dog.

5. Occasionally the mere introduction of a hypodermic needle into the spinal dural sac of non-anesthetized unoperated monkeys who have already received injections of 0.3 per cent. tricresol serum may produce a severe collapse. A preceding partial asphyxia seems to be a necessary condition.

6. Large quantities of sera are rapidly absorbed from the spinal dural sac of monkeys, and the clotting time of the blood is decreased.

7. The spinal meninges of the monkey seem very resistant to infection; even primitive precautions during intraspinal injections suffice to prevent infection.

8. Dogs are much more sensitive to the intraspinal injection of 0.3 per cent. tricresol serum than monkeys; nevertheless they may tolerate as much as 6 c.c. per kilo provided that intratracheal insufflation is maintained for some time after each injection.

9. The chief danger in dogs after intraspinal injections of 0.3 per cent. tricresol is a cessation of the respiration; for this reason artificial respiration of some type is necessary in this animal.

10. The blood-pressure in the dog may be profoundly lowered by 0.3 per cent. tricresol serum, yet recovery is usually obtained if intratracheal insufflation is maintained.

11. The effects of 0.3 per cent. tricresol serum upon the medullary centres is interpreted to be the result of either excitatory or inhibitory stimuli. No evidence was found that either the respiratory, vasomotor or vagus centre was paralyzed.

12. The local application of 0.3 per cent. tricresol serum upon the exposed medulla of dogs does not produce the same effect upon the respiration and blood-pressure as intraspinal injection of the same serum.

13. A solution of 0.3 per cent. tricresol serum applied locally to the medulla of dogs occasionally produces a transient respiratory stoppage, without markedly affecting the blood-pressure even when intratracheal insufflation is stopped.

14. Increased intraspinal pressure was found to be an important factor in the production of respiratory and blood-pressure changes in the dog after intraspinal injection of 0.3 per cent. tricresol serum.

15. Both in the monkey and in the dog 0.3 per cent. chloroform serum, 0.3 per cent. ether serum and plain horse serum produced in general a smaller effect upon the medullary centres than 0.3 per cent. tricresol serum.

16. The ideal preservative for therapeutic sera would seem to be one which could be removed before injection. Ether in this respect is better than chloroform.

17. The opsonins in antimeningitis serum are about equally affected by 0.3 per cent. tricresol, 0.3 per cent. chloroform and 0.3 per cent. ether when tested after one week, one month or three months.

18. When intraspinal injections are given in the human being it would seem advisable to be prepared to withdraw some of the injected fluid and to administer artificial respiration if necessary. For a safe withdrawal of fluid the gravity method is the best; for artificial respiration Meltzer's apparatus for pharyngeal insufflation can be recommended.

Addendum. After this paper was completed and ready for press an article appeared by Voegtlin[1] which demands consideration. Voegtlin's object was to study the quantitative effects of various tricresol serum concentrations on the blood-pressure and respiration when injected intraspinally in dogs and monkeys by the gravity method or by syringe; also to investi-

[1] Hygienic Laboratory Bulletin No. 96, 1914, p. 87.

gate the comparative effects of normal serum and of sera preserved by phenol, tricresol, formalin, and chloroform after intraspinal injection.

Voegtlin avoided the use of non-volatile anesthetics of the type employed by Hale in order to exclude their depressant effects upon the medullary centres; he substituted warm ether vapors which were administered to the animals through a tracheotomy wound. The respirations were recorded from the pleural cavity by means of a cannula and Marey tambour. The blood-pressure was taken from the carotid artery and a mercury manometer was used.

The intraspinal injections in the monkey were given in the usual way, that is, by introducing a needle through the skin and between the laminæ of the upper lumbar spinal column into the dural sac. In dogs, however, Voegtlin did not expose the cord by resecting the laminæ of the lumbar spinal column, a procedure which both Hale and I found necessary to secure uniform results, but he inserted the needle between two vertebræ after the spinal column was freely exposed. After obtaining spinal fluid, the needle was connected with a syringe or a burette depending upon the method employed for injection. When the gravity method was used a pressure of 40 to 50 cm. was found very satisfactory (p. 89).

From his investigation, which was largely confined to a study of the blood-pressure, Voegtlin comes to the general conclusions that the effect on the blood-pressure increases in proportion to the rate of injection and the concentration of the phenol preservative (p. 118); that there is no differences between the toxicity of phenol and tricresol serum of the same concentration (p. 116); that the fall of blood-pressure is primarily due to the inherent toxic action of the phenol or tricresol preservative on the medullary centres and not to increased intraspinal pressure, because the fall increases with an increase of the concentration (p. 116). He suggests chloroform as a preservative for antimeningitis serum because its intraspinal injection produced no dangerous effects (p. 118). He also recommends the use of the gravity method.

The experimental results which Voegtlin obtained with 0.3 per cent. tricresol serum, chloroform serum, and normal horse serum are in accord with those which my experiments have yielded, at least as far as they are shown by his illustrative tables and protocols. Indeed, his results with 0.3 per cent. tricresol serum and with chloroform serum were better than those which I obtained. With 0.3 per cent. tricresol serum Voegtlin publishes not a single death in either dogs or monkeys; the lowest level of the blood-pressure reached after a 0.3 per cent. tricresol injection was 55 mm. (Monkey 4, gravity method, p. 110) and the recovery of the blood-pressure was good in all recorded instances. The respiratory effect of 0.3 per cent. tricresol seems to have been slight in Voegtlin's dogs: a respiratory stoppage is nowhere noted in the protocols and only once is the respiration described as depressed (Dog 6, gravity method, p. 92). In spite of these good results from 0.3 per cent. tricresol serum which he has recorded in

his protocols, Voegtlin states (p. 115) that with 0.3 and 0.5 per cent. tricresol serum the respiration very often stopped after a dose of 3 to 5 c.c., that the blood-pressure fell to a low level and that this was followed by the death of the animal in a few minutes unless artificial respiration was given. Now the protocols and tables, which Voegtlin must have considered typical because he incorporated them in his article, do not support the above statement at all in its entirety but only as far as 0.5 per cent. tricresol serum is concerned. All the deaths in the protocols dealing with 0.3 per cent. tricresol were caused by the subsequent injection of 0.5 per cent. tricresol and never by 0.3 per cent. tricresol. As all my work with tricresol serum was limited to the 0.3 per cent. strength I am unable to discuss the effect of the 0.5 per cent. strength.

The effect on the blood-pressure caused by tricresol serum administered by the gravity method, Voegtlin interprets as primarily due to the inherent toxic property of this preservative and not to the increased intracranial tension (p. 116). While I am far from denying that 0.3 per cent. tricresol serum *per se* exerts an effect on the medulla, for my own experiments with local application of this solution to the medulla of the dog definitely show reactions, nevertheless I must point out that the experiments show a distinct difference between local medullary applications and intraspinal injections even if given by the gravity method. I have shown that the local application of 0.3 per cent. tricresol serum to the medulla, a procedure which practically rules out the element of spinal or medullary pressure, does not produce any marked effect on the blood-pressure, even when spontaneous respiration is abolished, as exceptionally happens (see Plate 11), yet the intraspinal injection of 0.3 per cent. tricresol serum even by the gravity method always produces a well-marked drop in blood-pressure (see Voegtlin, p. 92, 93). These differences show definitely that increased intraspinal pressure is a significant factor in the production of blood-pressure and respiratory effects after the intraspinal injection of 0.3 per cent. tricresol serum.

It must be emphasized in this connection that the gravity method is no guarantee at all that the intraspinal pressure is not raised by its employment, unless the rate of intraspinal absorption is as great as the rate of infusion. This condition is probably never fulfilled and the pressure in the gravity system is thus always greater than that in the dural sac of the cord for otherwise no serum would flow in. The degree of pressure used in the gravity method depends entirely upon the operator, Voegtlin for example used a pressure of 40 to 50 cm. of serum probably (p. 89). Such a pressure equals about 30+ mm. of mercury and this cannot be considered negligible for Voegtlin notes himself the appearance of pressure symptoms when normal serum was injected by this method (p. 114). That pressure plays an important role in the grave accidents which sometimes occur after 0.3 per cent. tricresol is well shown in Plate 8 of the present article where the mere removal of some cerebrospinal liquid sufficed to restore respiration and blood-pressure in a monkey. For these reasons I cannot agree with Voegtlin

when he states (p. 119) that he has shown conclusively that if a low rate of injection is used (gravity method) no pressure effects can be obtained with 0.3 per cent. tricresol, although his results with this concentration do warrant the belief that the pressure factor has been reduced by the gravity procedure.

Voegtlin always refers to the action of tricresol as toxic or depressant and apparently means that this substance damages the medullary centres (p. 115), but he gives no definite proof. In the body of this present paper I have advanced reasons why this view is probably not correct, but that on the contrary the tricresol, at least in 0.3 per cent. strength, acts as a stimulation to the excitatory and inhibitory functions of the medullary centres.

Voegtlin's results with the intraspinal injection of chloroform serum in dog by the gravity method were better than those I obtained by the syringe method in the same animal, but are quite comparable to those noted by me in the monkey (syringe method) and which are illustrated in Plate 5.

The only experimental discrepancy between Voegtlin's work and mine, where we deal with the same substances in the same strength, is with formalin serum. Voegtlin found 1 to 1000 formalin serum produced the same symptoms as phenol or tricresol injections of 0.25 to 0.5 per cent. strength. The few experiments made by me with 1 to 1000 formalin serum yielded a definitely smaller effect on the blood-pressure and respiration than 0.3 per cent. tricresol. I have already stated in the body of this paper that my experiments with formalin serum were not continued because formalin is a powerful coagulant and its action on the therapeutic properties of antisera is unknown.

DISCUSSION

Dr. Joseph A. Capps: I was very much interested in Dr. Auer's observations on the occurrence of shock from the simple introduction of the needle into the spinal canal, and if I understood him correctly this shock occurred not on the first introduction of the needle, but on the second, suggesting that the spinal membranes were irritated by the first injection and became sensitized. I would call attention to the analogy observed in the introduction of the needle in the pleural membrane and the occasional occurrence of shock. Dr. Lewis and I have observed that this rarely occurs in a normal dog on the first introduction of the needle, for instance, upon the injection of oil and turpentine to create artificial pleurisy. When, however, there is pleurisy present and the membrane is injected, the simple introduction of the needle will sometimes bring about shock. Similarly one might expect the symptoms of shock to occur more frequently from the introduction of a trocar into an inflamed spinal canal or one irritated by previous injections of serum, than in the canal of a healthy individual.

The recumbent position tends to prevent shock in thoracentesis and it would probably have a favorable influence in lumbar puncture.

Dr. S. J. Meltzer: This is an important practical subject. Therapy is the most essential part of medicine. With reference to serotherapy, I am inclined to believe that the antimeningitis serum has been more beneficial than any other antiserum; it has saved from 35 to 40 children out of every 100 cases of meningitis. The discussion which has been conducted in connection with the use of tricresol as a preservative, while correct in principle, may tend to obscure the situation; it is liable to divert attention from the actual importance of this method of treatment of meningitis.

Two suggestions are offered: one is to have no preservative at all, and the other is, to try other preservatives. From all we now know, one can guess that the percentage of deaths due to the contamination of the serum, when without a preservative, will be much higher than that due to the addition of tricresol. In this connection I need only quote Dr. Anderson of the Hygienic Laboratory, who a few months ago reported dangerous results from contamination of crotalin when used without a preservative. I shall refer also to the recent discussions in the German medical literature of the evil resulting from the contaminations of Friedmann's remedy. As to the use of other preservatives their harmlessness to the effectiveness of the antiserum as well as to the human organism has first to be established by extensive experimentation. We ought to be slow before we adopt other preservatives; we must be sure that they are better than tricresol. Of tricresol we know that it does not interfere with the effectiveness of the serum, and its dangers are very small, comparing them with the good which the serum accomplishes, the proportion being perhaps 0.01 per cent. to 40 per cent. The agitation against tricresol obscures this important practical proportion, and may perhaps cause one or the other physician to abstain from the use of the serum—to the detriment of the life of the poor little patients.

The experiments of Kramer, of Cincinnati, and of Hale from the Hygienic Laboratory, were made on animals which are very sensitive to the action of tricresol. Monkeys, as Dr. Auer found, are far less sensitive. The monkey stands much nearer to the human being than the dog or the cat. Furthermore, Dr. Auer found that even dogs need not die from even large doses of triscresol if efficient artificial respiration is used. In this connection I wish to call your attention to the method of artificial respiration by means of pharyngeal insufflation. The method is efficient and simple. I show you here the apparatus, but I shall not attempt to enter here upon detailed description of it.

THE PERSISTENCE OF ACTIVE LESIONS AND SPIROCHETES IN THE TISSUES OF CLINICALLY INACTIVE OR "CURED" SYPHILIS

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Between the pathologist and the clinician there is always a certain antagonism of attitude with reference to the curability of any given disease. The clinician is—and naturally must be—more or less optimistic as to the results of therapy; and only with the greatest reluctance is he convinced of the weakness or total failure of his therapeutic means and methods. The pathologist with the opportunities afforded him by tissue-examination and autopsy has the advantage of the very last word; and he becomes pessimistic as to ultimate cure because of his constantly recurring experience of finding evidences of active disease in cases clinically cured. This clash of opinion, clinical and pathological, is not elsewhere shown to such a degree as in the case of the venereal diseases, gonorrhoea and syphilis. It took much work on the part of the pathologist to convince the practitioner that clinically cured cases of the so-called "lesser disease" were only apparent cures, and that the gonorrhoea-infected individual remained for an indefinite period a germ-carrier, not only dangerous to himself, but much more so to his future sex-partner. Likewise in the case of syphilis therapeutic optimism has in recent years received severe blows at the hands of the pathologist. The frequency of latent syphilis of heart, aorta and central nervous system, the demon-

stration of spirochetes in conditions until very recently regarded as parasyphilitic in nature and etiology, thus proving these conditions to be still active infections, have somewhat shaken clinical optimism. Cures once promised after a year of active treatment, have passed through the two-, three- and five-year limit, and now some clinicians are advising the syphilitic to take interval treatment over a period of many years or even throughout his lifetime, if he will escape the uncertain chances facing everyone who acquires this disease. The wave of therapeutic optimism excited by salvarsan and the negative Wassermann reaction is even now subsiding.

It has been my experience as a pathologist to become very pessimistic as to the curative effects of any of the present day methods of treating syphilis. Before the spirochete became an absolute pathognostic sign of the presence of this disease, certain myocardial, aortic and testicular changes were regarded as well-nigh positive proof of syphilis. And the pathologist's judgment of these conditions is now confirmed by the demonstration of the spirochete of syphilis in such. Localized tissue-lesions of the smallest size and of the simplest nature that, a few years ago, would not have by any possibility been regarded as syphilitic have been shown to be evidences of the local presence of spirochetes. I have urged elsewhere the fact that our conceptions of syphilis, both pathological and clinical, must be reshaped, in the light of the spirochete; and that much work needs to be carried out along this line. The methods for the demonstration of this organism in the tissues should be made a part of the routine autopsy microscopical examination.

In my laboratory we have used Levaditi's original method with great success, and this is at the present time the only method of any value in demonstrating the presence of spirochetes in tissue. Its success will depend in the first place upon the freshness of the tissues. In my experience the spirochetes of syphilis quickly disappear from body-tissues after the body becomes cold. Our necessity of having to make autopsies very soon after death has been a very great advantage in this respect. Tissues taken from a warm body within one to two hours after death and immediately fixed in 4 per cent. formol for twenty-four to forty-eight hours,

then put through the Levaditi method and blocked in paraffin give the best results. When properly prepared the number of spirochetes at times demonstrable in the tissues of congenital and active acquired syphilis is incredibly large. In the case of latent syphilis the search for the organisms often becomes a prolonged hunt, and much time may be consumed in finding active lesions and demonstrating spirochetes within them. No one should think that this is wholly an easy matter. With an autopsy service of fifty to sixty cases a year the time of one assistant may easily be taken wholly for this work. Such an arrangement I have temporarily, but even with this advantage the work goes slowly enough. It may, however, be greatly expedited by confining the work to the organs, heart, aorta, testicles and adrenals, most commonly the site of latent syphilis, and by making control blocks of all parts of the organ or tissue for quick survey in ordinary hematoxylin and eosin staining. Should such control blocks show lesions recognizable as those possibly due to the localization of spirochetes, the corresponding block in Levaditi preparation is then examined first before a general examination of all the Levaditi blocks is made. If the blocks taken are small, as they should be, the neighboring Levaditi block is very likely to show some active process also. It may happen, however, that the hematoxylin and eosin sections alone show active lesions. The experiment of removing the paraffin and then putting the remaining portion of the block through Levaditi may be tried, but we have not found this procedure very satisfactory.

In the pathological service of the University of Michigan there were, from 1912 to 1914, 41 autopsy cases that on microscopical examination showed active syphilis, determined either by the presence of spirochetes or by characteristic tissue-lesions. In the latter the spirochetes are being demonstrated as fast as the work can be carried out; and this has already been accomplished to such an extent as to leave no doubt of the correctness of the diagnosis in all of the cases. The clinical history of a part of these cases gave no suspicion of the existence of a previous syphilitic infection; in others there was a doubtful or suspicious history of the disease;

while in a smaller number the patient had been treated, or was at the time of death undergoing treatment, for syphilis. In the majority of cases, it will be seen, the clinical diagnosis, and consequently the treatment entertained no suspicion of the existence of latent syphilis. In those cases in which syphilis was suspected or diagnosed the treatment in part had been regarded as adequate by patient and previous physicians, but a new course of treatment had been instituted after coming to the hospital. In a small number of cases the treatment had been more modern; the use of salvarsan had been thoroughly carried out, and the case regarded as clinically cured. As the taking of the Wassermann reaction has been made only during the last year a part of the regular examination routine for our hospital cases, it was made in the case of only a small number of those in whom syphilis was unsuspected. In the case of those in whom the infection was suspected or diagnosed it was regularly made.

I have accordingly divided the 41 cases into three classes: (1) cases in which there was a known history of syphilis, with treatment regarded as adequate and resulting in a cure; (2) cases in which the syphilitic infection was recognized as still active, treatment being continued; (3) cases in which a syphilitic history could not be obtained or was specifically denied by the patient, the clinical diagnosis not including syphilis and no antispyhilitic treatment given:

Class I.—Cases with History of Recognized Syphilis, Treatment, and Clinical Cure

1. Case C.—Aged sixty-two years. Chancre when a young man; treated by physician; never any other symptoms of the disease. No history of alcoholism. Wassermann not made. Clinical diagnosis of enlarged prostate. Operation. Death.

Path. Diag. Post-operative infection. Chronic purulent pyelonephritis. Old syphilis. Healed gummata of liver and testis. Orchitis chronica fibrosa syphilitica. Chronic epididymitis. Emphysema. Active syphilis in myocardium and aorta.

2. Case M.—Aged sixty-three years. "Cured syphilis." No symptoms since chancre when a young man. Clinical diagnosis of peritonitis following operation on bladder. No Wassermann.

Path. Diag. Post-operative peritonitis. Chronic cystitis. Papilloma of bladder. Chronic prostatitis and vesiculitis. Fatty degeneration of all organs. Bronchopneumonia. Active syphilis in myocardium, aorta and testes.

3. Case F.—Aged sixty-four years. No history of infection. Treated with mercury. "Cured." Blood gave a positive, and cerebrospinal fluid a negative Wassermann. Clinical symptoms cardiac. Question of aortic aneurysm.

Path. Diag. Mitral insufficiency and stenosis. Aortic insufficiency. Relative tricuspid insufficiency. Chronic parenchymatous nephritis. General atherosclerosis. Chronic passive congestion of all organs. Healed infarcts in lungs and kidneys. Thrombosis. Active syphilis of heart and testes.

4. Case K.—Aged forty-nine years (?). Sudden death following fracture of bones of leg. Cured syphilis when a young man. Chronic drinker. No Wassermann. Clinical diagnosis of embolism.

Path. Diag. Fracture of right tibia and fibula. Thrombosis of veins of right leg. Embolus in left pulmonary artery. Fat embolism of lungs. Early stage of alcoholic cirrhosis. Active syphilis in heart and aorta. Advanced syphilitis fibroid orchitis.

5. Case S.—Aged forty-five years. Chancre when young. Treated. Later tertiary recurrence. Treatment resumed. "Cured." Drinker. No Wassermann. Committed suicide with carbolic acid.

Path. Diag. Carbolic acid poisoning. Latent syphilis. Saddle-nose; gumma of spleen; active syphilis of heart, aorta, adrenals and testicles. Advanced orchitis syphilitica fibrosa.

6. Case M.—Aged seventy years. Syphilis when young man. "Cured." Chronic drinker. Clinical diagnosis of uremia. No Wassermann.

Path. Diag. Chronic parenchymatous nephritis. Chronic prostatitis, vesiculitis, pyelitis and cystitis. Localized chronic leptomeningitis. Coronary sclerosis. Hypernephroma of right kidney. Active syphilis in aorta, myocardium and testicles.

7. Case R.—Aged fifty-nine years. Date of infection not known. Treated. "Cured." No history of alcoholism. Wassermann negative. No clinical symptoms of syphilis. Clinical diagnosis of tumor of kidney.

Path. Diag. Hypernephroma of right kidney. Chronic parenchymatous nephritis, prostatitis, vesiculitis and cystitis. Old tubercles in bronchial nodes. Gummata of spleen and liver. Active syphilis of myocardium, aorta, spleen, liver and testes.

8. Case L.—Aged (?). Syphilitic infection twenty-three years ago. Treated with mercurials. "Cured." Chronic alcoholism. Died of croupous pneumonia. Both blood and cerebrospinal fluid gave a negative Wassermann.

Path. Diag. Croupous pneumonia. Syphilitic hepatitis. Syphilis of the aorta, heart, adrenals and testes.

9. Case Mrs. J.—Aged (?). Time of infection unknown. No clinical signs of syphilis. Blood and cerebrospinal fluid gave negative Wassermann. Diagnosis of nephritis.

Path. Diag. Chronic parenchymatous nephritis. Syphilitic aortitis. Fibroid heart. Chronic cystitis. Emphysema. Chronic vaginitis.

10. Case F.—Aged fifty-four years. Chancre at fifteen years of age. Treated. Never any other symptoms. Moderate drinker. Wassermann negative. Carcinoma of rectum.

Path. Diag. Adenocarcinoma of rectum. Secondaries in pelvis and peritoneum. General cachexia. Amyloid spleen. Syphilitic contracted kidney. Active syphilis of heart, aorta and testes.

11. Case G.—Aged forty-five years. Chancre twelve years ago. Treated. "Cured." Wassermann negative. Clinical diagnosis of chronic valvular disease.

Path. Diag. Aortic insufficiency. Aneurysm of ascending aorta. Active syphilitic lesions in heart, aorta and testes.

Class II.—Cases of Clinically Active Syphilis

12. Case W.—Aged (?). Date of infection unknown. Blood and spinal fluid gave positive Wassermann. Under treatment for syphilis of central nervous system. Died of pneumonia.

Path. Diag. Acute purulent bronchopneumonia. Active syphilitic aortitis and meningo-encephalitis. Fatty liver and heart. General marasmus.

13. Case T.—Aged forty-seven years. Denied syphilitic infection. Symptoms of tabes. No history of alcoholism. No Wassermann. Under antisyphilitic treatment.

Path. Diag. Active syphilitic leptomeningitis. Miliary gummata in cord and brain. Diffuse degeneration and sclerosis of cord and brain. Chronic parenchymatous nephritis. Active syphilitic lesions in heart and aorta. Orchitis syphilitica fibrosa.

14. Case H.—Aged forty-four years. Physician. Accidental infection nine years previously. Blood and spinal fluid gave positive Wassermann. Under active treatment. Early stage of paresis.

Path. Diag. Syphilis. Paresis. Acute purulent bronchopneumonia. Subacute parenchymatous nephritis. Acute purulent pyelitis. Chronic cystitis. General atherosclerosis. Active syphilitic lesions in brain, cord, heart, aorta, liver, adrenals and testicles.

15. Case W.—Aged forty-four years. Had hard chancre when 21 years old. Secondaries. Treated. Now shows early stage of tabes. Wassermann positive. Under active treatment.

Path. Diag. Syphilis. Tabes. Active syphilitic lesions in brain, cord, heart, aorta, liver and testicles. Acute parenchymatous nephritis. Chronic cystitis, vesiculitis and prostatitis. Healed tuberculosis of bronchial nodes.

16. Case S.—Aged forty-five years. Chancre fourteen years ago. Now symptoms of tabes. Wassermann positive. Salvarsan by intra-spinal injections. Arsenical poisoning.

Path. Diag. Syphilis of brain, cord, heart, aorta, pancreas and testes. Chronic interstitial nephritis.

Class III.—Syphilis Denied or not Suspected Clinically

17. Case G.—Aged sixty-three years. Denied venereal disease. No history of symptoms of syphilis. No Wassermann. No alcoholism. Clinical diagnosis of prostatic enlargement. Operation.

Path. Diag. Croupous pneumonia. Early stage of meningitis. Hypertrophy and dilatation of heart. Arteriosclerosis. Chronic parenchymatous nephritis and pyelitis. Chronic cystitis and prostatitis. Syphilitic lesions in heart, aorta and testes.

18. Case D.—Aged sixty years. No history of syphilis. No Wassermann. Clinical diagnosis cancer of stomach.

Path. Diag. Colloid carcinoma of pylorus. Chronic parenchymatous nephritis. Arteriosclerosis. Syphilitic lesions in heart, aorta, adrenals and testes.

19. Case Mrs. C.—Aged forty-five years. No history of syphilis. No Wassermann. Clinical diagnosis cystadenoma of ovary.

Path. Diag. Cystadenocarcinoma of ovary. Metastases in liver, spleen and regional lymph nodes. Syphilitic lesions in heart and pancreas.

20. Case Co.—Aged forty-three years. No history of syphilis or alcoholism. No Wassermann. Clinical diagnosis of tumor of intestines.

Path. Diag. Primary lymphosarcoma of intestine. Secondaries in mesenteric and retroperitoneal lymph nodes, kidney and liver. Chronic parenchymatous nephritis. Fatty cirrhosis of liver. Syphilis of heart, aorta, pancreas and testes.

21. Case S.—Aged sixty-eight. No history of syphilis. No Wassermann. No history of alcoholism. Clinical diagnosis of carcinoma of stomach and senility.

Path. Diag. Active syphilis of brain, cord, heart, aorta and testes. Early stage of paresis and tabes. Chronic prostatitis. Chronic parenchymatous nephritis.

22. Case Mrs. S.—No history of syphilis. No Wassermann. Dementia.

Path. Diag. Bronchopneumonia. Syphilis of heart and aorta. Coronary sclerosis. Fibroid heart. Biliary calculi. Adenomatous polyp of uterus.

23. Case Y.—Aged sixty-six years. Syphilis denied. No history of symptoms. No alcoholism. No Wassermann. Clinical diagnosis of myocardial insufficiency and coronary sclerosis.

Path. Diag. Active syphilitic myocarditis with cardiac thrombosis. Syphilitic aortitis. Multiple infarction of lungs and kidneys. Chronic parenchymatous nephritis. Early stage cirrhosis of liver. Syphilitic lesions in adrenals and testicles. Chronic prostatitis, cystitis, vesiculitis and pyelitis.

24. Case Mrs. Wa.—Aged (?). Doubtful history of syphilis. Never pregnant. Negative Wassermann. Clinical diagnosis of carcinoma of uterus. Death after operation.

Path. Diag. Carcinoma of uterus. Recurrence. Post-operative sepsis. Acute parenchymatous nephritis. Syphilitic lesions in heart and liver. Glissonian cirrhosis.

25. Case Mrs. B.—Aged twenty-four years. Treated by previous physician for syphilis. Syphilis excluded in hospital examination. Wassermann negative. Clinical diagnosis of chronic valvular lesions.

Path. Diag. Active late syphilis. Chronic syphilitic myocarditis and aortitis. Combined stenosis and insufficiency of mitral, aortic and tricuspid valves. Subacute parenchymatous nephritis. Multiple infarcts of lungs and kidneys. Severe anemia. Fatty liver. Syphilitic ulcer of leg. Gangrenous stomatitis, syphilitic with secondary infection. Colloid goitre.

26. Case M.—Aged fifty years. No history of syphilis. Negative Wassermann. Clinical diagnosis of thoracic aneurysm and carcinoma of stomach.

Path. Diag. Carcinoma of stomach. Syphilitic lesions in heart, aorta and testes.

27. Case K.—Aged (?). Denied venereal disease. Moderate drinker. Negative Wassermann. Enlarged prostate.

Path. Diag. Medullary carcinoma of prostate. Generalized metastasis. Addison's disease. Hydrothorax. Syphilis of heart, aorta and testes. Subacute parenchymatous nephritis. Chronic catarrhal gastritis. Hydrocele.

28. Case Mc.—Aged forty-four years. No history. Entered in toxic state. Suspected arsenical poisoning. No Wassermann.

Path. Diag. Acute alcoholic intoxication. Chronic alcoholism. Early stage of fatty cirrhosis of liver. Chronic parenchymatous nephritis. General atherosclerosis. Chronic pachymeningitis. Syphilis of testes.

29. Case G.—Aged thirty years. Denied venereal disease. Negative Wassermann. Moderate drinker. Clinical diagnosis of chloroma.

Path. Diag. Primary carcinoma of pancreas; metastases in vertebræ, retroperitoneal glands, mesentery, adrenals, testes, and bronchial nodes. Syphilis of testes.

30. Case Mrs. B.—Aged (?). No history or symptoms of syphilis. Wassermann negative on blood, 4 + on spinal fluid. Eight months pregnant. Clinical diagnosis of tuberculous meningitis. Miscarriage. Dead fetus.

Path. Diag. Lobar pneumonia. Chronic tuberculosis of bronchial nodes. Miliary tuberculosis of lungs, liver, spleen and peritoneum. Cascation of one adrenal. Syphilis of myocardium and of fetal chorion.

31. Case B.—Aged forty-two years. Gonorrhea at twenty years of age. Denied syphilis. Wassermann negative. Drinker. Clinical diagnosis of alcoholic cirrhosis.

Path. Diag. Alcoholic cirrhosis. Syphilis of heart, aorta and testes.

32. Case W.—Aged seventy-eight years. No history of syphilis. Wassermann positive. No clinical diagnosis.

Path. Diag. Syphilis of heart, aorta, pancreas and testes. Syphilitic peribronchitis. Chronic parenchymatous nephritis. General marasmus.

33. Case B.—Aged forty-eight years. No history of venereal diseases. Wassermann negative. Clinical diagnosis of prostatic enlargement and uremia.

Path. Diag. Primary carcinoma of prostate. Metastases in liver. Chronic cystitis, ureteritis and pyelonephritis. Syphilis of heart, aorta and testes. Fatty liver and adrenals. Pulmonary edema. General atrophy. Emphysema. Infected cystotomy wound.

34. Case E.—Aged (?). No history of syphilis. No Wassermann. Clinical diagnosis of diabetes. Mitral insufficiency.

Path. Diag. Diabetes. Atrophy of pancreas. Dilatation of heart. Purulent bronchopneumonia. Subacute parenchymatous nephritis. Syphilitic orchitis.

35. Case Ar.—Aged forty-eight years. No history of syphilis. Wassermann negative. Diagnosis of diabetes. Sepsis.

Path. Diag. Diabetes. Infected squamous-celled carcinoma of finger. Ascending purulent lymphangitis of right arm. Septicemia. Syphilis of heart, aorta, pancreas and testes.

36. Case Al.—Aged sixty-nine years. Denied venereal disease. Wife had one miscarriage. Drinker. Wassermann not taken. Diagnosis of croupous pneumonia, and pernicious anemia.

Path. Diag. Croupous pneumonia. Syphilis of heart, aorta and testes. Syphilitic contracted kidney. Anemia gravis. General atrophy.

37. Case Mrs. Bo.—Aged forty-four years. No history of syphilis. Never pregnant, no precautions taken. Wassermann negative. Died of general peritonitis.

Path. Diag. Acute purulent peritonitis. Infected laparotomy wound, post hysterectomy. Syphilis of heart and adrenals.

38. Case W.—Aged fifty-five years. Denied venereal disease. Moderate drinker. One Wassermann test negative, second one positive. Diagnosis of alcoholic cirrhosis.

Path. Diag. Alcoholic cirrhosis. Ascites. Portal stasis. Syphilis of heart, aorta and testes. Emphysema. Chronic prostatitis.

39. Case J.—Aged seventy-two years. Denied venereal disease. Moderate drinker. Wassermann negative. Clinical diagnosis of myocardial insufficiency.

Path. Diag. Aortic insufficiency and stenosis. Sclerosis of endocardium. Mitral stenosis and insufficiency. Cardiac hypertrophy and dilatation. Syphilis of heart, aorta, pancreas and testes. Syphilitic ulcer of leg. Emphysema. Brown induration of lung with multiple infarcts. Early interstitial nephritis. Early stage of alcoholic cirrhosis. General atrophy.

40. Case C.—Aged fifty-nine. Denied venereal disease. No Wassermann. Clinical diagnosis arthritis deformans of spine. Terminal pneumonia. Pyelonephritis.

Path. Diag. Primary scirrhous adenocarcinoma of prostate with metastases in vertebræ, ribs, pelvic bones, lungs, liver, and retroperitoneal lymph nodes. Aspiration purulent bronchopneumonia with abscesses of lung. Multiple abscesses in kidneys. Chronic cystitis. Syphilis of heart, aorta, adrenals and testes.

41. Case Ca.—Aged forty-five years. Denied venereal disease. One Wassermann test negative; second one positive.

Path. Diag. Croupous pneumonia. Chronic ulcerative colitis with multiple polyp formation. Chronic dysentery. Amyloid spleen. Syphilis of heart.

It will be seen from the above list that there are 11 cases with clinical diagnosis of recognized and treated syphilis regarded clinically as cured, 5 cases of active syphilis under treatment for symptoms of the disease, and 25 cases in which a diagnosis of syphilitic infection was excluded clinically because of absence of symptoms and denial of previous infection. It is very probable that some of the patients in this third group were actually in total ignorance of any infection. In the case of the women it is practically certain that this was the case. Some of the male patients in this group no doubt had had the primary sore so long before that they

had either forgotten it or no longer attached any importance to it. Having long ago accepted that condition as cured, they consider it as past history and deny that it ever took place. It is, of course, a very common experience in dealing with patients of this type to, receive repeated denials of the occurrence of syphilitic infection, and the information of such an infection must be drawn out by special and prolonged tactics of questioning.

In all of these 41 patients the lesions of active syphilis were practically of the same nature, whether in cases that had been treated, or were being actively treated or had received no treatment at all. Active syphilitic lesions were found in the heart in 36 cases, in the aorta in 32, in the testes in 31, in the liver in 4, in the adrenals in 6, in the spleen in 1 case, pancreas in 5 cases, and central nervous system in 5 cases. As five of the patients were women, and deducting these, the lesions in the testes occur as frequently as those in the heart. The organs most frequently the seat of acitve lesions in order of frequency of occurrence would be aorta, heart, testes, adrenals, pancreas, central nervous system, liver, and spleen. It is also of great interest to note that of these patients there were 16 cases of subacute or chronic parenchymatous nephritis; 2 of acute parenchymatous and 5 cases of interstitial nephritis, although no relationship between the syphilis and the kidney lesions can be positively affirmed. The preponderance of cardio-vascular-renal symptoms in the cases on the whole may be taken as evidence of the important etiologic rôle of syphilis for such symptoms, and lead the clinician to consider always the possibility of syphilis in such cases. In 12 of the 25 cases of clinically unsuspected syphilis, spirochetes have been demonstrated beyond question.

In the determination of the existence of syphilitic infection in any given case coming to autopsy the heart, aorta and testis in the male are the organs that should receive the most thorough examination. If latent syphilis is present active lesions will be found in one or the other of these organs if they occur anywhere within the body. The triad of interstitial myocarditis, aortitis and orchitis fibrosa may be taken as a pathologic complex indicating the occurrence of a syphilitic infection. In medicolegal work these

three organs should be chosen in preference to all others for microscopic examination when the question of syphilis is concerned.

The problems of latent syphilis are certainly emphasized by these studies. The apparent symbiosis of spirochetes within such organs as the heart, aorta and testes through a period of many years without causing greater damage or giving rise to more marked symptoms must be taken as proof that the organisms have a very low virulence in such cases. "Cured" syphilis in many cases, if not all, is but a latent infection or symbiosis with spirochetes that have a very low virulence, in some cases not much greater than that of the intestinal flora. It becomes increasingly important to know the conditions under which organisms remaining so relatively inactive over long periods of time may at times renew their aggressiveness and cause more marked damage.

The therapeutic lesson is evident. Promises of cure within definite time-limits can never be safely made, and our advice as to treatment must include the possibility of treatment extended over many years. The latency of the infection seems to be the same in many untreated cases as in those receiving very good treatment. From the standpoint of eugenics it may also be said that absence of symptoms, or even of history of infection, and negative Wassermann reaction cannot in any degree be looked upon as indicating freedom from latent syphilis.

DISCUSSION

Dr. William H. Welch, Baltimore: Dr. Warthin has presented to us a very important communication, but there is one point which comes up for consideration. Considering the evidence we now have of reinfection with syphilis, I would like to ask him if he thinks a patient, after having been cured of syphilis on clinical grounds, can acquire chancre and be reinfected? That has been regarded as proof of actual cure and I still regard it as a proof of cure.

Dr. Warthin (closing): There is no sign of reinfection in any of these cases, and there is absolutely no history of that kind. These cases must be considered, so far as the material I have carefully gone over is concerned, as beyond the possibility of reinfection. As I am very doubtful about the possibility of a cure of syphilis, I also am doubtful concerning reinfection, in spite of the few reported instances.

THE EFFECT OF RADIUM ON SPONTANEOUS CARCINOMATA IN MICE

By FRANCIS CARTER WOOD, M.D
NEW YORK

Despite the extensive use of radium and mesothorium in the treatment of malignant growths, a decision as to the ultimate therapeutic effect, based upon the published clinical reports, is not possible at the present time. While it is quite certain that radium and mesothorium may, for a time at least, favorably influence some of the benign types of epithelioma which occur about the face and scalp, it is equally certain that it does not act as effectively on the more malignant tumors of the mucous membranes and internal organs, and that its action does not extend for any great distance into the substance of the tumor, certainly not more than 5 cm.

The reasons for this lack of accurate information are not far to seek. In the first place, satisfactory quantitative measurements of the strength of radium or mesothorium preparations have become possible only recently; secondly, in many reported cases the nature of the growth has not been determined microscopically, and all of these reports must be discarded; and thirdly, but few of the supposedly cured cases have been followed for the minimum period of three years before being reported as cured. A recurrence after a clinical "cure" by radium has been noted eight years after the treatment was instituted.

The many difficulties which attend the investigation of the effects of radium on human tumors, and the impossibility of accurate operative or autopsy control of the results, led me to begin a series of experiments on the action of radium on spontaneous tumors in mice. So far as I am aware no extended experiments have previously been made except with transplanted tumors, the frequency

of whose spontaneous regression introduces a factor difficult to estimate. Bashford[2] states that the regression of a primary tumor from the action of radium has never been observed, but he gives no further information.

The most important reports on the effect of radium on transplanted tumors are the following: Apolant[1] was able to cause complete resorption of transplanted tumors in five out of seven mice. In the controls only two out of six ceased to grow actively. In a second series, three cures were obtained in eight mice; while in ten controls there were two spontaneous cures. The tumors used were carcinomata in the seventh and eighth generations. Twenty mg. of radium were employed, but the report does not state whether this was estimated as salt or as element, possibly it was the bromide ($RaBr_2 + 2H_2O$).

Bashford[3] used 10 mg. of radium bromide and solutions of radium emanation. Out of eleven animals the tumor in two showed a slight diminution in size, in three a marked diminution; and in one it was almost completely absorbed in nineteen days. In one animal, twenty-seven days after the first exposure, the tumor had grown rapidly. Out of fourteen animals which received injections of an aqueous solution of radium emanation, the tumor disappeared in two, and diminished in three. After injections of radioactive normal saline solution in seven animals, the tumor grew in two, was unaltered in one, diminished in two, and disappeared in one. The animals used all had inoculated tumors.

In 1910 Maud Menten[10] reported the results of radiating a series of white rats bearing grafts of the Flexner-Jobling carcinoma. In a large number of animals exposed to various strengths of radium preparations complete disappearance was noted in a few, but these cures were not larger in number than might occur spontaneously in animals bearing these tumors. In mice bearing the Jensen sarcoma the tumor disappeared in 6 out of 8 cases. The Ehrlich mouse sarcoma was not affected by the radium.

More recently, Krönig and Gauss[7] have reported that no effect on mouse carcinoma can be obtained by the use of large quantities of radium, varying between 15 and 100 mg. of bromide, because the general action on the animals is so severe that death occurs

before the tumor is influenced. While no statement is made, it is probable that the tumors treated were inoculated carcinomata and not primary growths. The writers say that this shows that a mouse carcinoma may possess a special resistance to radiation more than is possessed by human carcinoma.

Lazarus[9] observed great diminution in the size of transplanted tumors in two mice treated with 100 mg. of mesothorium screened with 2 mm. of lead and 0.5 mm. of nickel, giving one hundred hours of treatment. Neither tumor, however, was completely destroyed.

Keysser[6] states that the treatment of animals with "100 mg. of 50 per cent. mesothorium" had a beneficial action only on superficial and ulcerating tumors of mice. The mesothorium was used both screened with lead and unscreened. No effect was produced in less than 800 mg. hours. Although no definite statement is made it is evident that the work was done on transplanted tumors.

Lawrence[3] reports the cure of several small inoculated tumors by the use of small quantities of radium. The exact amount of radium used cannot be determined from the report.

Wassermann[12] also calls attention to the fact that it is very difficult to influence mouse carcinomata with the rays of mesothorium, which exert the same biological effects as those of radium. He was unable to destroy such carcinomata by direct exposure to 50 mg. of mesothorium, while with the same quantity it was possible to destroy the ultimate viability of carcinoma cells *in vitro* in three hours.

It is practically certain, however, that primary mouse carcinomata are no more malignant than many tumors in man; for, as a matter of fact, spontaneous regressions occasionally occur in these animals, while they are of the utmost rarity in man. It may be, nevertheless, that mouse carcinoma is more resistant to radium than are certain types of the human growth.

My own experiments show a marked influence exerted by radium on spontaneous tumors of mice. While a number of the animals died during treatment, from the general action of the radium on the body, marked changes occurring in the organs, especially the spleen and bone marrow, in some though not all of the animals which survived for a sufficient length of time the tumor was reduced in

size to a minute remnant of cells. In no case, however, was a cure effected on a primary tumor. That the cells are no more susceptible than those of normal tissue of the same type is shown by results of radiations *in vitro* of growing cultures of tissue cells.[13] Practically no difference in susceptibility exists. Rapidly growing tumor tissue in man or animals is, however, in many, though not in all, instances more susceptible than the neighboring healthy adult connective tissues to the rays from radium.

It is probable that a part at least of the effect of radium upon animal tumors *in situ* is not upon the cancer cell itself, but upon the bloodvessels, causing thrombosis, hemorrhage, and consequent necrosis. Only when repeated exposures to large quantities of radium have been made is the growth of the cells themselves interfered with, and even in this case my own studies, which are as yet incomplete, do not point toward the probability of ultimate cure. Of course, it is not possible absolutely to transfer these results to human beings.

The methods of applying radium are as follows: The solid salt, screened or unscreened; the emanation, in glass tubes; or a solution of the salt or emanation.

The Radium Institute, London, has for some time been using radium emanation in the treatment of tumors.[11] This method has also been used by Duane in connection with the work of the Cancer Commisssion of Harvard University, and by John Joly in conjunction with W. C. Stevenson.[5] The sole advantage of the application of radium emanation lies in the fact that the entire energy of the radium may be pumped off and concentrated in a thin glass tube of less than 1 c.c. capacity. This tube will stop the alpha rays, but all the beta and gamma rays are free to act upon the tissues. Such thin tubes can be implanted in a tumor and will give 25 to 30 per cent. more energy than the corresponding tubes of radium salts with the filters necessary to protect the skin and neighboring healthy tissues. It is also possible to deposit the decomposition products of radium emanation on steel plates and apply these directly to the surface of a carcinoma. Most of those who are now working with radium use glass tubes of the salts screened with 1 to 3 mm. of lead, platinum, gold, aluminum or brass.

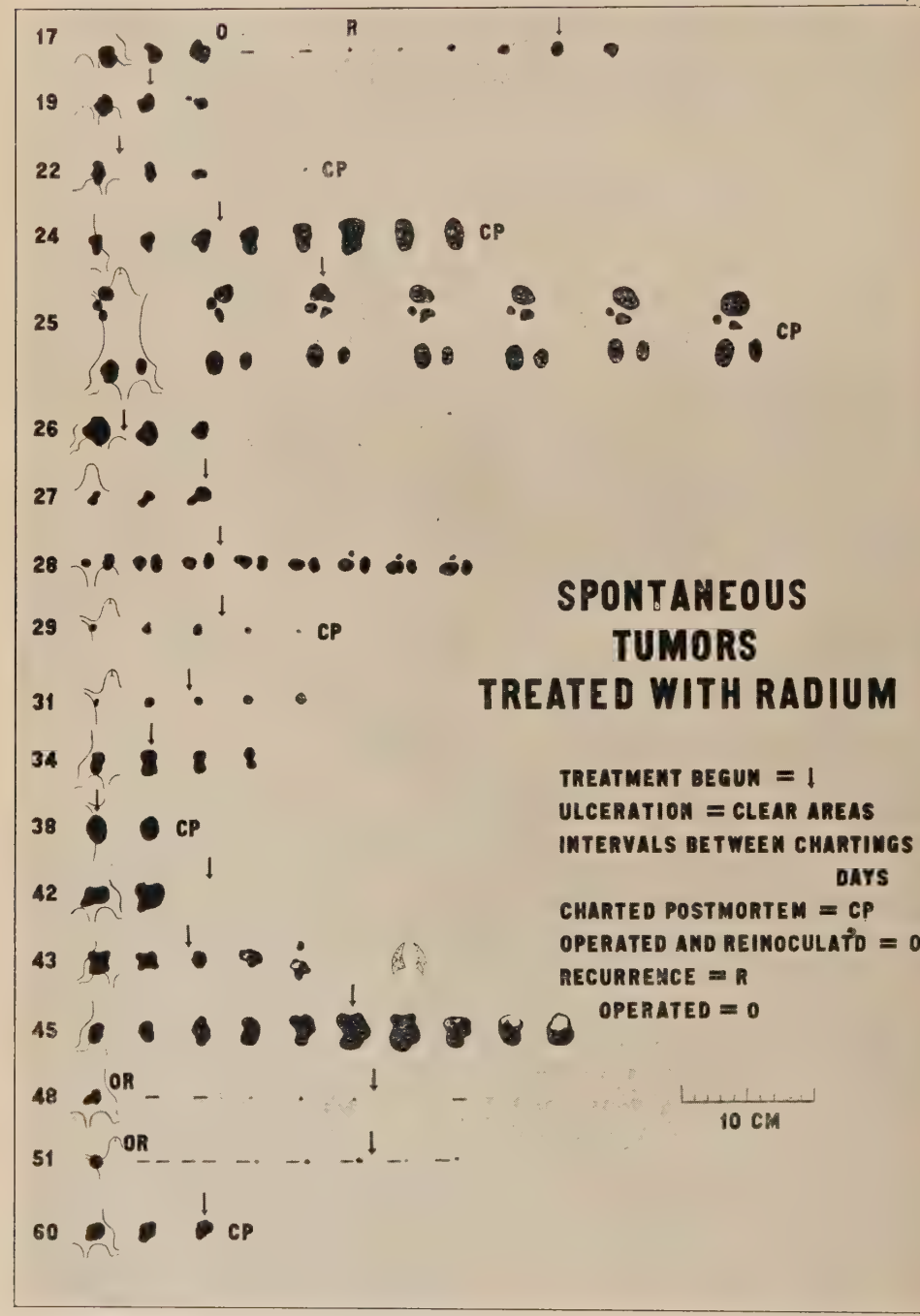
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FIG. 1

In my own experiments the animals were, with few exceptions, treated directly with radium in tubes, generally unscreened, as the skin of the mouse is much less susceptible to the burning effects of radium than that of human beings. The exceptions were one case in which an emanation tube was planted directly in the tumor, and two cases in which the tumor was treated by direct injections of radium sulphate into the growth. The chart (Fig. 1) shows the results, the system used being that devised by Gaylord and familiarized by Bashford. The numbers on the chart correspond with those in the protocols. The tumors were charted every seven days, and their relative dimensions are accurately reproduced.

A few protocols are appended to give details as to the length of the treatment, the screens used, and the microscopic appearance of the tumors.

Mouse 17/0. Radium treatment of recurrent tumor. Mouse with six spontaneous tumors. As it was impossible to treat all of these tumors with radium they were all excised on December 20, 1913, and examined microscopically. A recurrence of one tumor was noted on January 17, 1914. This was allowed to grow in order to determine whether regression would take place spontaneously. On February 14 the tumor had grown to a considerable size, measuring 8 x 11 mm. On that date, noted on the chart by an arrow, 83 mgm. of radium element in a 2 mm. platinum tube and five thicknesses of hardened filter paper (S & S. No. 575) were laid in close contact with the tumor for one hour and thirty-five minutes.

February 15. Same treatment repeated for one hour.

February 19. Same treatment repeated for one hour.

February 21. The tumor showed distinct evidences of growth. 83 mgm. of radium element, unscreened except by the thin glass tube container, were applied directly to the tumor for one hour and ten minutes.

Five days later (Feb. 26) the animal was found to be dying, and was killed. Postmortem examination showed the tumor to be a flat, oval, hard mass, adherent to the skin of the thorax. On section the tissue was pale yellow, and very firm. There were no hemorrhagic areas in the tumor. The rectum and sigmoid were contracted, and neither contained any feces. There was a subcutaneous hemorrhagic area in the left axilla near the tumor.

Microscopic examination showed that this tumor, which when first excised was an adenocarcinoma (Fig. 2), was altered into a sarcoma-like growth (Fig. 3), no recognizable epithelial cells being present. Interpretation of the condition is difficult. We may suppose (1) that the epithelial cells were so modified that they assumed a connective-tissue shape at the

site of the tumor; (2) that the radium destroyed the epithelial cells and induced a sarcoma by its stimulating action on the connective-tissue cells, as shown by the experience of Clunet[4] who observed the development of a sarcoma after an *x*-ray burn in a white rat. The tissues of these inbred tumor animals are very sensitive to trauma of all sorts, and sarcoma not infrequently develops after bites and other injuries. Or (3) that the recur-

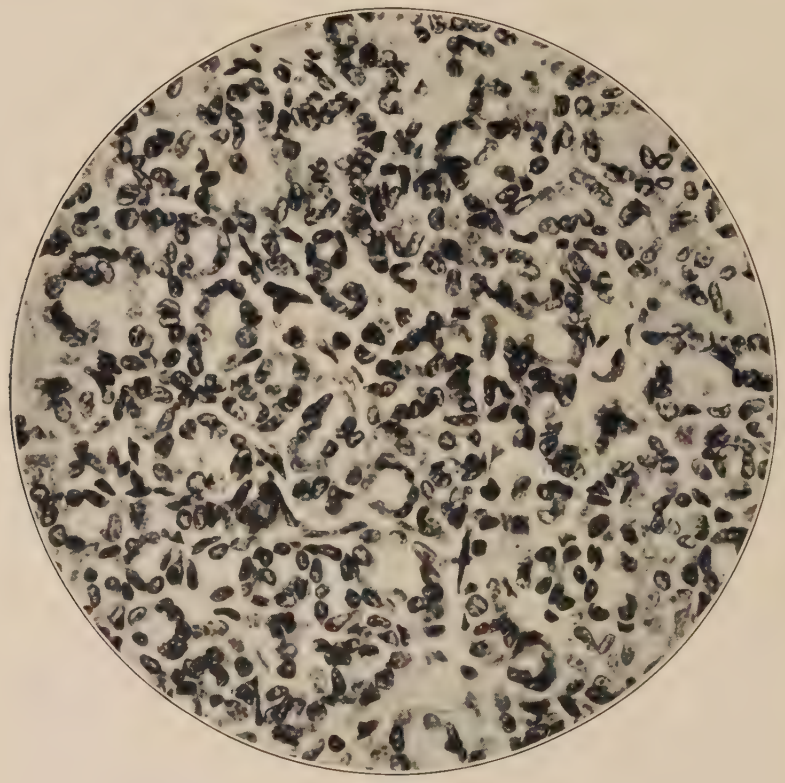

FIG. 2.—Adenocarcinoma of breast of mouse. × 500.

rence after excision was a sarcoma derived from the tumor stroma, in line with the observations of Bashford and Ehrlich that a carcinoma may change into a sarcoma; or (4) that it was a granuloma. As no transplants of the tumor were made after it was removed, it is not possible to decide whether it was or was not a malignant growth, except on a morphological basis.

Mouse 19 0. Mouse with tumor involving the rectum and the left side of the abdomen, and measuring 16 x 13.5 mm.

December 27, 1913. 17 mgm. of radium element inclosed in a glass tube were attached to the mouse by adhesive plaster and left in contact with the tumor for forty-eight hours. On its removal the animal showed no evidence of illness and there was no ulceration of the tumor.

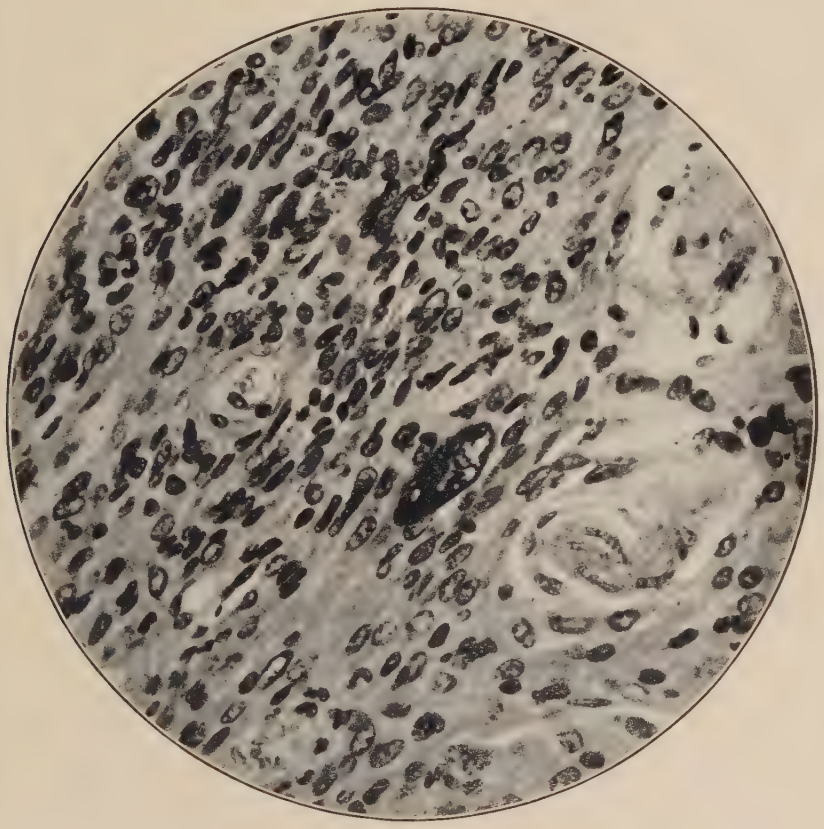

FIG. 3.—Sarcoma-like growth following radium treatment of recurrence of tumor shown in Fig. 2. × 500.

January 6, 1914. In order to control the morphology of the tumor a small fragment was excised for microscopic examination. The tumor was found to be very cystic and to contain a large amount of chocolate-colored fluid. The animal died during the operation, having lived only ten days after the radium treatment was instituted. The tumor had shrunk considerably, as is shown on the chart.

Microscopic examination showed growing carcinoma on the walls of the cavity, the cells showing numerous mitoses.

Mouse 22/0. Tumor measured 8 x 11 x 19 mm., and occupied the region of the rectum and the vulva on the right side of the abdomen.

January 21, 1914. 83 mgm. of radium element, covered with 1 mm. of black rubber tubing, were applied to the surface of the tumor for one hour.

January 22, 23, 24, and 26. This treatment was repeated for one hour each day.

February 7. The animal was found to have died during the night. The tumor had shrunk, as shown in the chart, only a small nodule, 2 mm. in diameter, being discoverable at the site. The skin was badly burned and a deep ulcer occupied the site of the tumor.

Microscopic examination (No. 219) showed that the remnant of the tumor lay in a mass of connective tissue infiltrated with small round cells and many phagocytic cells bearing pigment. The vessels were intensely congested, especially the small capillaries, and there were many areas of hemorrhage in the new connective tissue. Part of the tumor showed a tendency toward keratinization with the formation of masses of large syncytial cells. Other areas showed perfectly typical adenocarcinoma with many mitoses.

Mouse 24/0. Cystic tumor, measuring 18 x 7 mm., in the left groin.

February 2, 1914. 83 mgm of radium element in 1 mm. platinum tube, covered with three thicknesses of tissue paper and 1 mm. of black rubber tubing, were applied to the tumor for forty-five minutes.

February 3. Treatment was repeated for fifty minutes.

February 5. 17 mgm. of radium element, covered with 1 mm. of black rubber tubing and a layer of zinc oxide adhesive plaster, were applied to the tumor for one hour.

February 6. Treatment was repeated for one hour.

February 11. 17 mgm. radium element in a 2 mm. platinum tube were applied for one hour.

February 25. As the tumor was rapidly increasing in size, 83 mgm. of radium element, unscreened except for one layer of zinc oxide adhesive plaster, were applied for five hours. The tumor was slightly reduced in size (see Chart).

March 6. The animal was found dead. The tumor was a mere bag of blood, and the tissue was too badly decomposed to give satisfactory sections.

Microscopic examination (No. 428) showed that the tumor was almost entirely altered into a sac filled with blood and necrotic tissue. The new growth was preserved only around the bloodvessels and at the periphery where the tumor cells still adherent to firm subcutaneous tissue retained their characteristic morphology. The capsule of the tumor was edematous and much infiltrated with small round cells and in some places was entirely necrotic. In other places a much altered epidermis was still present.

Mouse 25/0. Animal had five large tumors.

January 31, 1914. Tumor on right side of neck was exposed for ten minutes to 83 mgm. of radium element in glass tube only.

February 3. 17 mgm. of radium element, covered with 1 mm. of black rubber tubing, were applied for one hour.

February 4. Treatment was repeated for one hour.

February 11. 83 mgm. of radium element in a 2 mm. platinum tube and covered with thirty layers of tissue paper, were laid in a small box with the mouse for four hours.

February 12. This general treatment was repeated seven hours and thirty minutes.

February 13. Treatment was repeated for six hours.

February 23–24. As all of the tumors were growing, the general treatment was repeated for fifteen hours and forty-five minutes; on

February 24–25, repeated for fifteen hours and twenty-five minutes; and on

February 25–26, repeated for fifteen hours and thirty minutes. The treatment thus approximated forty-seven hours in three days.

February 27. Animal died at 3 P.M. The tumors were all charted after death and, allowance being made for natural shrinkage due to lack of vascularity, no effect of the radium could be shown. All of the masses, except one which was firm and healthy looking, were soft and fluctuating, and were filled with chocolate-colored fluid.

Microscopic examination (No. 368) showed that in the spleen the lymphatic structures were atrophied and replaced by connective tissue. But few megakaryocytes were present. A few hematoidin crystals were seen.

The tumor which had received special treatment was found to consist almost entirely of a blood filled cyst. Attached to the firm connective tissue of the capsule there were areas of unaltered carcinoma showing some necrosis and in places pycnosis of the nuclei. No mitoses were found. The other tumors showed no effects from the radium. The kidneys were very much altered and congested, the cells staining poorly, the glomerular tufts being thickened, and the nuclei pycnotic. There was occasionally hyperplasia of the capsular cells. The liver showed some necroses, diminution in the number of liver cells, intense congestion and infiltration with leukocytes, and prominence of the capillary endothelium. The spleen was much altered; there was rarefaction of the splenic elements, hemorrhagic areas, a large number of phagocytes, and many megakaryocytes.

Mouse 26/0. The tumor (adenocarcinoma) involved the rectum and vulva, and measured 22 x 11 mm.

January 22, 1914. 83 mgm. of radium element in 1 mm. of black rubber tubing were applied to the surface of the tumor for one hour.

January 23. Treatment was repeated for one hour.

January 24. Treatment was repeated for one hour and ten minutes. The tumor was slightly smaller.

January 26. Treatment was repeated for one hour.

January 27. Treatment was repeated for forty-five minutes. The tumor area was badly burned.

January 31. The animal died four days after the last treatment. The previously solid tumor was converted into a cyst with thin walls and filled with dark grumous material. The skin over the tumor was thickened, injected, and adherent.

Microscopic examination (No. 163) showed enormous hemorrhages into the substance of the tumor and connective tissue. In these hemorrhagic areas the cells of the carcinoma were almost completely destroyed and necrotic, or else a considerable portion of an alveolus contained necrotic cells. Other parts showed cells with normal structures. A large number of phagocytes containing blood pigment were scattered throughout the tissue. Some parts of the tumor showed adenocarcinoma of approximately typical structure. Mitoses were scanty. The nuclei still looked like those of the ordinary carcinoma cells. Syncytial forms were not present. The connective tissue instead of being inflamed was rather hyaline and scantily cellular. The capillaries were intensely distended.

Mouse 27/0. Animal had two tumors, one in the neck measuring 12 x 5 mm., and one in the groin, measuring 20 x 17 mm. Both tumors grew progressively from January 19 to January 31, when treatment was begun.

January 31. 83 mgm. of radium element, unscreened, were applied to tumor of neck for forty-five minutes, and to the inguinal tumor for five minutes.

February 2. Two days after treatment the animal died. At autopsy a large cheesy mass was found in the abdomen. The spleen was greatly enlarged. The neck tumor, which had been exposed to the radium, was soft and hemorrhagic. The inguinal tumor was firm. There were no macroscopic lesions in the other viscera.

Microscopic examination (No. 169) showed that the neck tumor was softened and hemorrhagic; the peripheral portion still showed adenocarcinoma unaffected by the radium as far as could be made out morphologically. There was edema and chronic inflammation of the stroma of the tumor in the groin, but no other changes. A metastatic nodule was present in the lung.

Mouse 28/0. The animal had two tumors in the groin which grew progressively from January 17, 1914, when it was received, until treatment was begun.

February 2, 1914. 83 mgm. of radium element in 1 mm. platinum tube, applied to tumors for twenty-five minutes.

February 21. Tumors had not changed in size, but a new tumor had appeared.

February 24. 83 mgm. of radium element, unscreened, were applied to tumors for two hours.

March 7. The mouse was sick and was killed. The tumor on the right side was filled with brown hemorrhagic fluid. The tumor on the left side was firm, with a few hemorrhagic areas. There were firm inflammatory adhesions about both tumors. The organs were normal in the gross.

Microscopic examination (No. 430) showed, with the exception of a rather intense hemorrhagic and inflammatory reaction in the connective tissue and fat surrounding the tumors and some thickening of the walls of the bloodvessels, no lesions which could be attributed to the effect of the radium.

Mouse 29/0. Animal had small tumor in right axilla, measuring about 5 mm. in diameter. The tumor grew progressively from January 17, 1914, when the mouse was received, until treatment was begun on February 3.

February 3, 1914. 83 mgm. of radium element in glass capsule, unscreened, was applied to the tumor for one hour and ten minutes.

February 4, 5, and 6. The treatment was repeated for one hour and five minutes, one hour and thirty minutes, and one hour, respectively.

February 7. The tumor was much smaller.

February 13. The animal was found dead. The tumor measured 2 mm. in diameter. At autopsy the site of the tumor was found to be very hemorrhagic and the tumor was soft and yellowish. The right lung, which was nearer to the radium, was voluminous and congested. The left lung was collapsed. The right pleural cavity contained bloody fluid.

Microscopic examination (No. 262) showed that the skin over the tumor was badly burned. The connective tissue was edematous, with many hemorrhages and thromboses in the smaller vessels. In many of these vessels also there was very great swelling of the capillary endothelium. The muscle fibers near the irradiated area showed a myositis. There was a great deal of old blood phagocyted by cells in the connective tissue. The tumor was considerably altered; it was edematous and showed the characteristic changes which follow extreme radiation; that is, the formation of syncytial masses with great irregularity in the size and chromatin richness of the nuclei (Fig. 4). An occasional mitotic figure could still be seen, showing that all the cells had not lost their power of proliferation. A small sebaceous epitheliema which was discovered in the groin accidentally at autopsy, showed the usual type of this tumor: very little epithelium and large cavities filled with sebaceous material and desquamated epithelium. The spleen was very much atrophied and showed extensive areas of hemorrhage with phagocyted blood pigment and many megakaryocytes. The lymphoid structures had practically disappeared. The bone marrow was apparently not altered by the action of the radium. The liver was slightly fatty and showed a good deal of acute degeneration. It contained a large number of nucleated hemoglobin-bearing cells which looked like megalocytes. There was a good deal of leukocytic infiltration, some chronic con-

gestion, and in one area a focal necrosis. The right lung showed a moderate irritation pneumonia with extensive hemorrhages into the alveoli.

Mouse 34 0. Animal with tumor of right groin, measuring 17 x 10 mm. The tumor grew rapidly from February 5, 1914, when it was received until February 14, when treatment was begun.

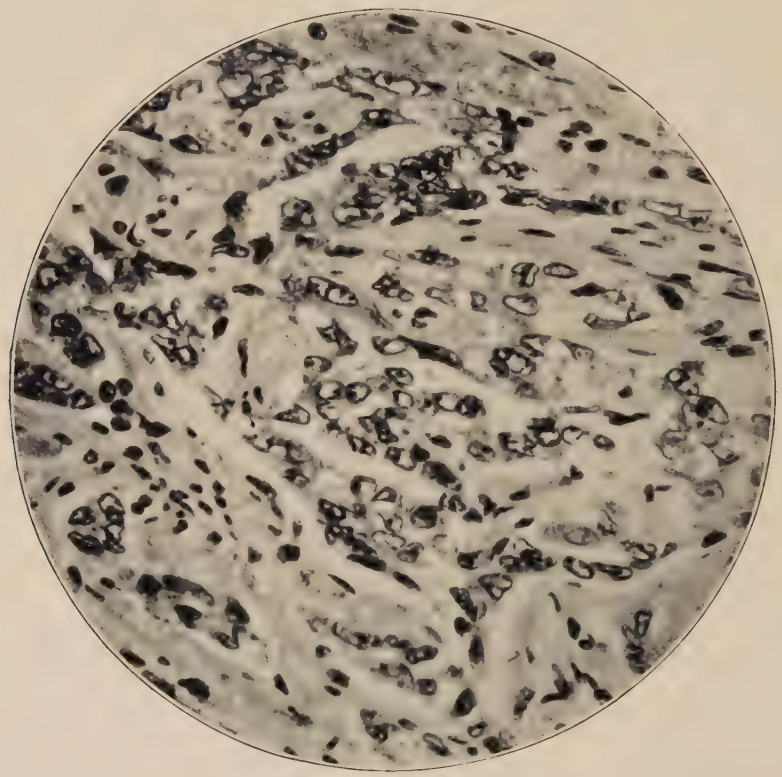

FIG. 4.—Shrinkage and syncytium formation as the result of radium applications. × 500.

February 14, 1914. 83 mgm. of radium element in 21 mm. of platinum tube and five thicknesses of hardened filter paper were laid in a small box with the mouse for eighteen hours and thirty minutes.

February 25. Tumor had decreased in size. 83 mgm. of radium element, unscreened, were applied directly to the tumor for two hours.

February 26. Treatment was repeated for one hour and thirty minutes.

March 3. The mouse died. The tumor was filled with dark hemorrhagic fluid. There was no inflammatory congestion about the tumor.

The intestines contained bloody fluid. The lungs were very firm and mottled with red hemorrhagic areas. The spleen was very small.

Microscopic examination (No. 391) showed that the tumor was a hemorrhagic adenocarcinoma with a tendency toward keratinization in some portions. In the keratinized areas there was a little necrosis. In the areas of adenocarcinoma the cells were microscopically typical. The bloodvessels of the interstitial tissue were congested and in a few areas there were hemorrhages into the connective tissue. There was also a very small amount of connective tissue reaction with the formation of fibroblasts. This was seen especially in the area where hemorrhages had occurred. The kidneys showed a distinct cloudy swelling with distention of the Malpighian tufts and a few hemorrhages in the kidney substance. Some of the tubules were filled with blood and some contained casts. The spleen showed extensive alterations; the lymphocytic structures had largely disappeared and had been replaced by fibrous tissue. There were a very large number of phagocytes containing blood pigment. The megakaryocytes occasionally found in a mouse spleen were very scanty. The lungs showed distinct congestion with the escape of red cells into the alveoli. The lung contained a metastatic nodule of the same type as the primary tumor. The liver showed a very extreme fatty degeneration, but little of the liver substance remaining. The bronchial lymph nodes were atrophic and contained large pigment-bearing phagocytes.

Mouse 38/0. Tumor in right axilla, measuring 21 x 15 mm.

February 28. A small glass tube, about 1 mm. in diameter and 4 mm. in length, and containing 16 millicuries of radium emanation equivalent to 16 mgm. of radium element, was inserted under aseptic precautions into the middle of the tumor. The animal remained in apparent health for eight days and was then found dead in its cage.

On removal of the tumor there was no evidence of any shrinkage in size. There were no apparent lesions in the viscera. The right lung was macroscopically normal. The tumor was dry and sebaceous. There were no hemorrhagic areas.

Microscopic examination (No. 408) showed the tumor to be of the sebaceous type. The central portion showed almost total necrosis at the area where the emanation tube lay. Only a few nuclei retained any staining power at the periphery. There still remained a good many alveoli with cells which retained good staining power and normal morphology (Fig. 5). The capsular connective tissue showed hemorrhagic areas and a growth of new connective tissue cells. There were also a moderate number of phagocytes. Some of this connective tissue was even necrotic. The action of the emanation was evidently very powerful, but much of the necrosis was similar to that seen spontaneously in these sebaceous tumors and was not necessarily due to the radium. The lungs were markedly congested, with hemor-

rhages into a few of the alveoli. The kidneys showed cloudy swelling, hemorrhages into the Malpighian tufts, lymphocytic and plasma cell infiltration along the line of some of the bloodvessels, and numerous casts in the tubules. The splenic tissue was badly damaged and was intensely hemorrhagic, and contained a large number of phagocytic cells and megakaryocytes. The liver showed enormous congestion and infiltration with many leukocytes. A portion of the surface was necrotic.

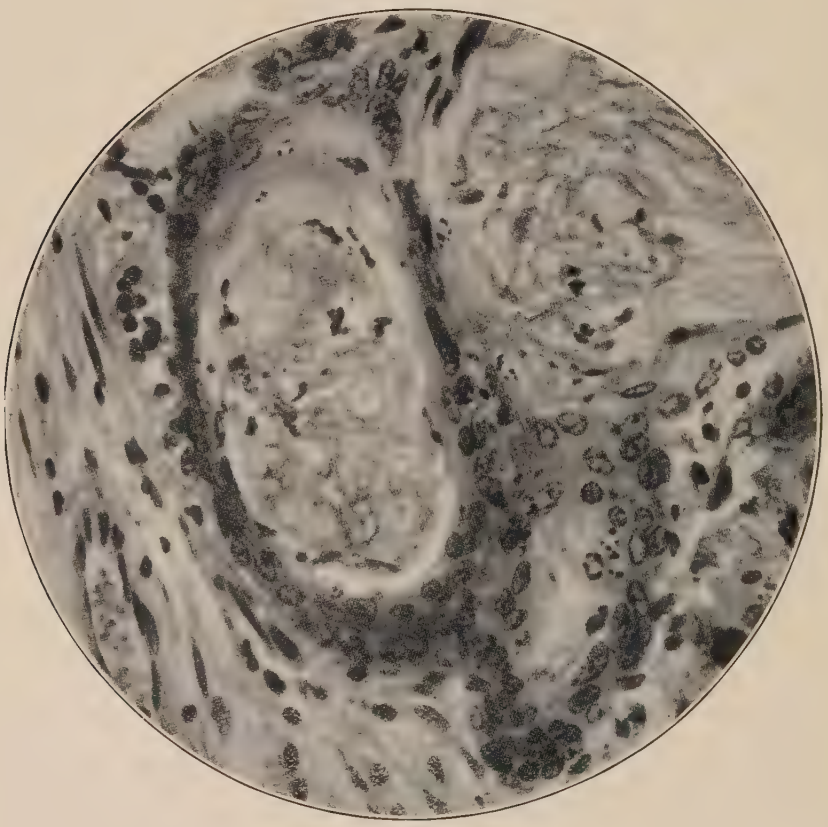

FIG. 5.—Showing result of treatment with 16 millicuries of radium emanation on sebaceous carcinoma of the mouse. Well-preserved peripheral portion. × 500.

Mouse 43/0. Animal with tumor in right groin, measuring 17 x 17 mm. roughly. The tumor increased in size from February 28, 1914, when the animal was received, until March 13, when treatment was begun.

March 13, 1914. 17 mgm. of radium element, unscreened, was applied to the tumor for one hour.

The tumor softened in the centre and a few days later was washed out with sterile salt solution so as to remove the products of tissue destruction, as it was thought that some of the animals previously treated might have died from a toxemia induced by the large amount of protein material absorbed from the tumors. Such toxemias, even followed by death, have been noted in human beings treated with radium, and the enormous mass of these tumors as compared with the body weight of the animal would give a much larger absorption in the mouse than in man. The animal remained healthy for eighteen days and then died. The tumor had shrunk somewhat during this period. The lungs were filled with enormous numbers of metastases.

Microscopic examination (No. 588) showed that the tumor was converted into a sac filled with blood, with much necrosis of the tumor tissue in the central portion. At the periphery, however, there were well preserved carcinoma cells showing no microscopic change. The lungs were filled with necrotic metastases. There was also a metastasis in the heart muscle, showing extensive necrosis. It is probable either that the mechanical disturbance due to the washing out of the tumor set free particles which metastasized, or that the prolongation of the life of the animal because of the irrigation gave time for the production of metastases. It is rare to find an animal so extensively involved as this.

The two following cases are examples of the treatment of recurrences or reimplantations in the original host.

Mouse 48/0. Animal with tumor in left groin, measuring about 13 x 8 mm. This was removed at operation on March 17, 1914, and a transplant was placed in the right axilla. The transplant grew and on April 22 measured about 2 mm. in diameter. It was then treated with 83 mgm. of radium element, unscreened, at 1 cm. distance for two and a half hours. Eight days later it was treated with the same amount at the same distance for two hours. The tumor disappeared and had not reappeared at the death of the mouse on June 16.

A recurrence of the groin tumor was, however, noted on May 16. On May 29 this tumor had reached a diameter of 3 mm. It was then treated with 83 mgm. of radium element, unscreened, in contact with the tumor for three hours. This mass likewise disappeared. The mouse died on June 16. The burns from the radium and the resulting inflammation made it impossible to recognize any tumor, but the site of each was excised and serial sections were made. The main tumor showed a small oval mass, measuring about 1 x 0.5 mm., containing a number of cells apparently much altered. These were loose in the connective tissue, not closely related to the bloodvessels, and the whole gave the appearance of cells which were

not active. No mitoses could be found. The axillary tumor had disappeared in the same way; the sections showed no trace of a neoplasm.

This result corresponds with that seen in human beings, as it is quite easy to cure superficial small metastatic nodules with radium, while the primary tumor absolutely resists such treatment.

Mouse 51/0. The primary tumor was operated on and reimplanted. Morphologically (No. 508) the tumor was a hemorrhagic adenocarcinoma. On April 22, 1914, 83 mgm. of radium element, unscreened, were applied to the tumor at a distance of 1 cm., for three hours.

The mouse died on May 19. The lungs were congested and there was a little chronic pleurisy. There were large lymphoid collections about the bronchi.

Microscopic examination (No. 874) showed that the tumor had been converted into a small cyst lined with eithelium. At one portion there was a crescent shaped area of carcinoma showing mitosis and no structural abnormalities.

Conclusions. 1. It is not possible to cure primary tumors of mice with the quantities of radium and the methods employed in this study.

2. It is possible to destroy subcutaneous metastases in mice as in human beings by the use of large doses of radium.

3. Mouse carcinoma is not more resistant to radium than is human carcinoma.

4. The injection of small amounts of radium sulphate into the substance of a tumor has no permanent influence upon its growth.

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A FURTHER REPORT OF THE PATHOLOGIC EVIDENCE OF THE RELATIONSHIP OF GASTRIC ULCER AND GASTRIC CARCINOMA

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Introduction. The following report is a continuation of a study of gastric ulcers and cancers first presented to this society in 1909.[1]

Between January 1, 1905, and January 1, 1914, tissues were received for examination in the laboratories of the Mayo Clinic from 870 gastric and duodenal cases.[2] From 705 of these cases the tissue included the site of the primary lesion. Of these, 260 were simple chronic ulcers without histologic evidence of cancer. Most of these ulcers have recently been critically examined by MacCarty.[3] Therefore the gross material and sections from only a small number of the ulcers have been examined by us for comparison with those from the cancer cases. The present review has been largely confined to the study of the gross and microscopic tissues from the 445 gastric carcinomas received in the laboratory during the nine years above mentioned. Of these, 399 specimens were resected by the surgeon and 46 were removed at autopsy from cases on most of which an exploratory or palliative operation had been done.

Data. The data for the following report is based on (*a*) the primary pathologic diagnoses made from the examination of the

[1] Wilson and MacCarty, Amer. Jour. Med. Sci., December, 1909, pp. 846–852.

[2] During the progress of this study a portion of the data with a slightly different and less accurate tentative grouping was presented before the St. Joseph County Medical Society, South Bend, Indiana, and later published in the Collected Papers from the Mayo Clinic, 1913.

[3] Arch. Int. Med., 1914, vol. xiii, pp. 208–222.

specimen immediately after its removal, in almost all instances, either by one of us (Wilson) or by MacCarty. This examination included in all cases of at all doubtful character a microscopic examination of frozen sections. (*b*) The review of all photographs of the entire specimens and of microscopic sections taken at the time of the primary pathologic diagnosis. (*c*) The review of all sections of fixed tissues previously prepared from the cases. (*d*) From many cases the study of serial paraffin sections recently prepared and selected to include, wherever possible, a section through the border and base of the ulcerating lesion. (*e*) A study of the clinical data as regards length of period of previous symptoms and as regards subsequent history. This data has been kindly supplied by Drs. Graham and Eusterman.

Classification of Cases. All cases in which there was suggestive or positive evidence of cancer have been placed in four groups, as follows:

1(?). Ulcer with cancer questionable.
1. Ulcer with beginning cancer.
2. Ulcer with advanced cancer.
3. Cancer throughout the lesion.

Group 1(?).—Group 1(?) consists of those cases in which a most painstaking study of the sections gave evidence which was only suggestive of early cancer. The interpretation of the histologic pictures would, no doubt, vary with different observers. In general, it may be said that the suspicion of cancer rests upon profuse aberrant proliferation of the gastric epithelium and, in some instances, on suggestions of infiltration of individual cells or groups of cells into the surrounding tissue. Where infiltration can be accurately determined there should be no question about the presence of cancer. Where it is doubtful, we must express that doubt. Among the cases in this group is the following:

Case I.—86829. S. H. F., female, aged forty-one years. History of chronic gastric ulcer seven years; more severe for last six months. Wide excision of supposed gastric ulcer July 7, 1913. Pathologic diagnosis, gastric ulcer. In fair condition six and one-half months after operation. (See Figs. 1 to 3.)

The significance of such cases from the clinical standpoint lies in

the fact that of the nineteen in our series three patients have subsequently died of gastric cancer. In all of these, practically all of the small gastric ulcer was examined microscopically and no evidence beyond such as that seen in the above case was found.

FIG. 1.—Case I. 5-diameter magnification of section from border of ulcer.

The first of these patients, Case II–5957P, P. J. M., was a male, aged fifty-eight years, who for six years had had symptoms of chronic gastric ulcer. On December 3, 1906, a portion of the stomach was removed for a supposed gastric ulcer. Pathologic diagnosis was doubtful cancer on ulcer. Patient lived three years and one month after operation, dying of recurring gastric carcinoma.

The second patient, Case III–A10131, S. J., was a male, aged sixty-three years, giving a history of chronic gastric ulcer covering a period of two years. May 30, 1908, a partial gastrectomy with excision of a perforating gastric ulcer was done. Patient died of recurring gastric carcinoma twelve months later.

Fig. 2.—Case I. 50-diameter magnification of area marked *B* in Fig. 1.

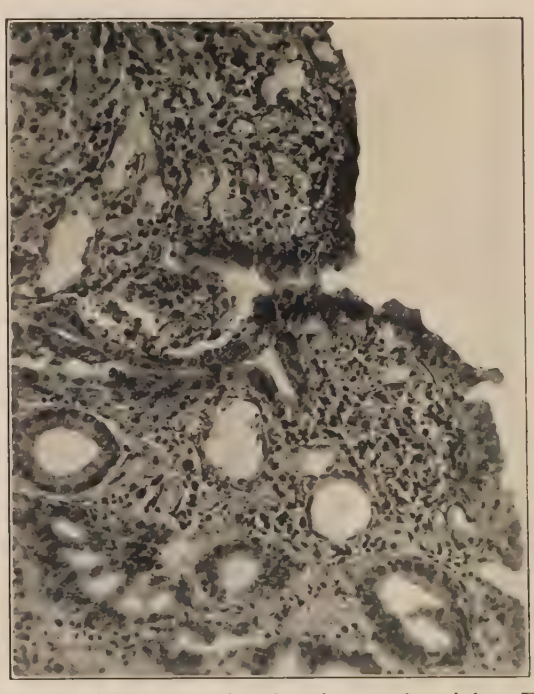

Fig. 3.—Case I. 150-diameter magnification of area selected from Fig. 2, showing markedly proliferating epithelium with doubtful infiltration.

The third patient, Case IV–15038, T. G., was a male, aged fifty-nine years, who had had symptoms of chronic gastric ulcer ten years. September 24, 1908, there was a partial resection of the lesser curvature of the stomach for chronic gastric ulcer. Primary pathologic diagnosis of the tissue removed was ulcer. Patient returned two and one-half years later with an inoperable carcinoma of the stomach, from which he died two years and nine months after his first operation.

Group 1.—In Group 1 are placed those cases in which the epithelium is not only aberrantly proliferating but also undoubtedly infiltrating the surrounding tissues and yet in which, on the other hand, the base of the ulcer is free of carcinomatous tissue and gives no evidence of ever having contained such. The following cases will serve to illustrate this group:

Fig. 4.—Case V. 5-diameter magnification of section from border of ulcer.

Case V.—28092. W. F. S., male, aged fifty-seven years. History of chronic gastric ulcer for three years; carcinoma, one and

FIG. 5.—Case V. 50-diameter magnification of area marked *B* in Fig. 4.

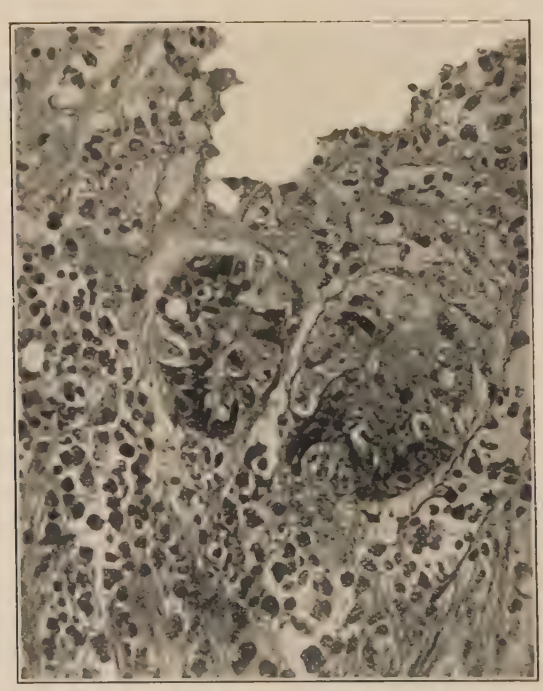

FIG. 6.—Case V. 300-diameter magnification of border area shown in Fig. 5. Note the two groups of cells, the cancerous nature of which is typical though their infiltration is not plain.

one-half months. Resection three-fifths of stomach June 3, 1910. Pathologic diagnosis, early cancer on ulcer, glands not involved. Dead in thirty-six months after operation of recurring gastric carcinoma. (See Figs. 4 to 6.)

Fig. 7.—Case VI. 6-diameter magnification of section across ulcer.

Case VI.—53784. H. M. S., male, aged forty-five years. History of chronic gastric ulcer for nineteen years. Gastric carcinoma for three months. Resection of two-thirds of stomach June 8, 1911. Primary pathologic diagnosis, early cancer on ulcer; no involvement of glands resected. Patient reported in good condition twenty months after operation. (See Figs. 7 to 9.)

Group 2.—The cases included in this group are the cases in which the cancer has more or less invaded the base of the ulcer, and yet in which a well-defined portion of the ulcer remains free of cancer. It is concerning the cases in this group about which most discussion has developed among pathologists, certain observers holding that it is impossible to distinguish in these cases between the development of cancer in the base of an ulcer and the erosion of cancerous tissue forming an ulcer which contains no evidence of epithelium.

FIG. 8.—Case VI. 50-diameter magnification of point marked *B* in Fig. 7.

FIG. 9.—Case VI. 600-diameter magnification of group of cells showing early carcimona selected from area shown in Fig. 8.

It seems to us, however, that it is possible in many instances to differentiate between the two conditions, and we have placed in this group only those cases about which we have felt certain that the condition was the former. When a sharp border-line exists between the infiltrating epithelium and the scar tissue and when, at the same time, the cancer tissue lies in an antomic plane external to the scar tissue, it would appear that the evidence is preponderatingly in favor of the supposition that the scar tissue existed before the development of the cancer and consists of the remains of the base of a pre-existing gastric ulcer. The following cases will serve to illustrate this group:

Fig. 10.—Case VII. 5-diameter magnification of section through border to base of ulcerated portion.

Case VII.—59396. J. D. H., male, aged sixty-five years. History of chronic gastric ulcer for twenty-five years; of gastric carcinoma eleven months. Resection of portion of stomach October 3, 1911. Pathologic diagnosis, cancer on ulcer; three glands on

FIG. 11.—Case VII. 50-diameter magnification of area marked *B* in Fig. 10, showing sharp borderline which exists between ulcer and carcinoma in an advanced case.

FIG. 12.—Case VII. 150-diameter magnification of carcinomatous area in Fig. 11.

lesser curvature involved. Patient died one month after operation. (See Figs. 10 to 12.)

Case VIII.—33130. E. W., male, aged thirty-nine years. History of chronic gastric ulcer for many years; of gastric carcinoma one year. Partial gastrectomy January 26, 1910. Pathologic diagnosis, carcinoma on ulcer; one gland in greater curvature involved. (See Figs. 13 to 15.)

Fig. 13.—Case VIII. 2-diameter magnification of section through base of ulcer.

Case IX.—29584. W. C., female, aged forty-nine years. History of chronic gastric ulcer for many years; gastric carcinoma two and a half months. One-half of stomach resected October 8, 1909. Pathologic diagnosis, cancer on ulcer. Patient died of gastric carcinoma six months after operation. Case shown to illustrate that even in advanced gastric carcinoma there may be sometimes found areas in base of ulcer which are free of carcinoma and give no evidence of ever having been invaded. (See Figs. 16 to 18.)

FIG. 14.—Case VIII. 50-diameter magnification of area marked *B* in FIG 13, showing sharp borderline between ulcer and carcinoma.

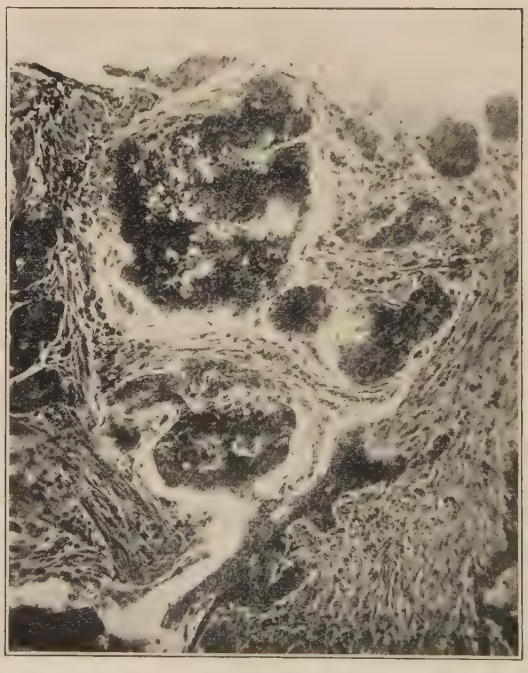

FIG. 15.—Case VIII. 150-diameter magnification of carcinomatous border of section shown in Fig. 14.

These scar-tissue bands extend through to the muscularis. When one studies the structure of the gross specimen in relation to the microscopic section, the impression is very strong that these cancer-free scar-tissue areas are not the result of the destruction of the epithelium as we know does occur in scirrhus cancer elsewhere, but that these masses of scar tissue have been formed prior to the development of the infiltrating epithelium in their neighborhood.

FIG. 16.—Case IX. 2-diameter magnification of section through base of ulcer. Almost the whole of this section, except the area marked *B*, is infiltrated with carcinoma.

CASE X.—69652. G. E., male, aged forty years. History of chronic gastric ulcer for ten years; gastric carcinoma one month. One-third of pyloric extremity of stomach resected July 1, 1912. Pathologic diagnosis, carcinoma on ulcer. Patient in good condition seven months after operation. (See Figs. 19 to 21.)

GROUP 3. This group contains those cases of cancer in which the evidence of previous ulceration is absent or incomplete. In a

FIG. 17.—Case IX. 50-diameter magnification of area free from cancer shown at *B* in Fig. 16.

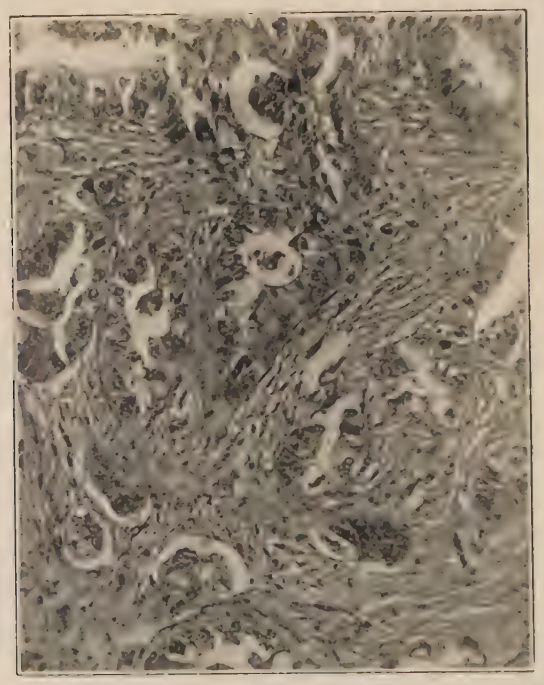

FIG. 18.—Case IX. 100-diameter magnification of area just lateral to that shown in Fig. 17.

very few instances, less than 5 per cent., is the evidence entirely absent. In almost every case in the series there is ulceration, in some portion of which may be found a tract of scar-tissue clear of carcinoma, in many instances penetrating through the muscularis and side by side with areas of cancer which lie in anatomic planes internal to the scar-tissue. Such a condition is seen in the following case:

FIG. 19.—Case X. 4-diameter magnification of section through border and base of ulcer.

CASE XI.—27585. Male, aged sixty-three years. History of chronic gastric ulcer extending over many years. History of cancer extending over a period of three months. Resection of pyloric two-thirds of stomach September 18, 1909. Pathologic diagnosis, carcinoma with extensive glandular involvent. Patient died three months after operation. (See Figs. 22 to 24.)

Such a case as this has always been interpreted as ulcerating cancer. However, from the preponderance of cases in which the reverse has been true of the order of development, it would appear

FIG. 24.—Case XI. 150-diameter magnification of cancerous portion of tissue.

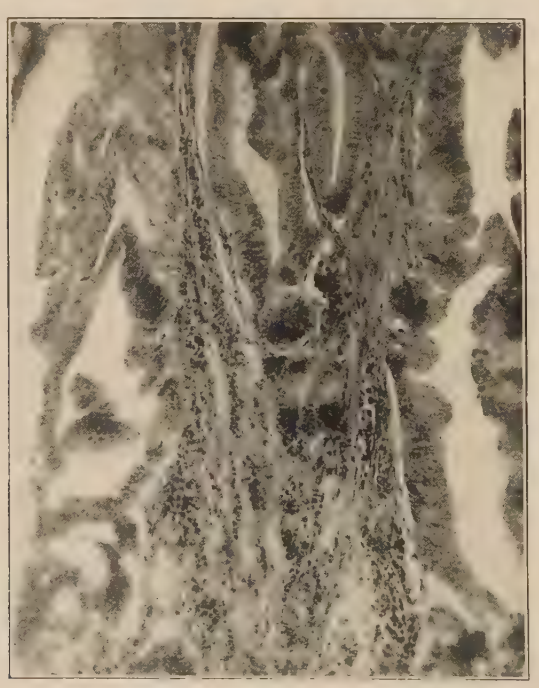

FIG. 25.—Case XII. No. 52034. 100-diameter magnification of section from papillomatous cancer of pylorus.

questionable whether we have the right to assume that cases of this kind are illustrations of ulcerated cancer. Indeed, when one considers the clinical evidence in relation to a careful histologic study of a large series of operative cases of gastric cancer, he is led to the opinion that, in all probability, very few cases of gastric cancer exist which have not taken their origin at the site of a previous ulcerative lesion of the mucosa. It is only in rare instances, not more than four or five in our entire series, in which there appears a rapidly growing fungating papillomatous cancer of the pylorus in which no previous ulcerative lesion is suggested. It must be remembered that, even in these, a small chronic ulcer of the pylorus may have been literally covered in by the rapidly growing mucosa. Such a case as this is our Case XII–52034. (See Fig. 25.)

TABLE I.—ANALYSIS OF CASES IN WHICH SPECIMENS INCLUDED THE SITE OF GASTRIC ULCER OR CARCINOMA. CASES OPERATED ON

	Ulcer	Group 1 (?) Ulcer +Ca.?	Group 1 Ulcer + early Ca.	Group 2 Ulcer + Adv. Ca.	Group 3 Ulcer ? + cancer.
Total number . . .	170	19	63	147	170
		(4.8%)	(15.8%)	(36.8%)	(42.6%)
Average age at operation	43	51	50	50.9	54.7
Percentage of cases giving chronic history . . .		(58.0%)	(8.5%)	(70.7%)	(48.8%)
Average number of years of chronic history . .		9.1	9.0	11.1	13.2
Percentage of cases giving severe recent history .		67.0%	82.5%	89.0%	90.6%
Average number of months of acute history . . .		2.5	4.5	5.0	6.0

Table I contains an analysis of the cases of this series operated on. In the first column are grouped 170 cases of gastric ulcer which are given for purposes of comparison. It will be noted that the average age at operation of these patients was forty-three years, while the average age at operation of the patients with positive ulcer and questionable early or advanced cancer (Groups 1(?), 1, and 2) was approximately fifty years. At the same time the average age of the 170 patients in the tissues of whom there was undoubted cancer with incomplete evidence of previous ulcer (Group 3) was 54.7 years. These clinical data so far as they go, are in harmony with the pathologic findings that gastric ulcer first develops and cancer is implanted thereon, and that, after the latter disease proceeds, it obliterates the evidence of previous ulcer.

When one remembers the numerous instances of advanced gastric cancer which have given no symptoms until within a period of a few weeks prior to death, he is struck with the high percentage of cases between 70 and 80 per cent. (Groups 1(?), 1, and 2) which gave a history suggesting gastric ulcer and extending over a period averaging from nine years in the early cases to eleven years in the advanced cases. Group 3 shows that only 48.8 per cent. of the cases in which previous ulceration was questionable gave a history of long previous gastric ulcer, though of the cases which did give a history the average period of symptoms was over thirteen years.

Sixty-seven per cent. of the cases of ulcer with questionable carcinoma gave histories suggesting carcinoma extending over an average period of two and a half months; 82.5 per cent. of the cases of ulcer with early carcinoma gave histories suggesting gastric cancer extending over an average period of four and a half months; 89 per cent. of the cases of ulcer with advanced carcinoma (Group 3) gave histories suggestive of cancer extending over an average period of five months; 90.6 per cent. of the cases of cancer with questionable ulcer gave a history suggestive of cancer extending over an average period of six months. These data are interesting in relation to a study of 566 consecutively operated and pathologically demonstrated cases of cancer of the stomach in our Clinic (Smithies[1]).

TABLE II.—ANALYSIS OF CASES IN WHICH SPECIMENS INCLUDED THE SITE OF GASTRIC ULCER OR CARCINOMA. AUTOPSY CASES

	Ulcer.	Group 1 (?) Ulcer +Ca?	Group 1 Ulcer + early Ca.	Group 2 Ulcer + Adv. Ca.	Group 3 Ulcer ? + cancer.
Total number	15	1	...	7	38
		(2.2%)	...	(15.2%)	(82.6%)
Average age at operation or autopsy		57.0	...	54.7	54.1
Percentage of cases giving chronic history		...	...	...	50.0%
Average number of years of chronic history		9.0	...	4.0	7.9
Percentage of cases giving severe recent history		...	...	...	76.0%
Average number of months of acute history		1.0	...	2.8	4.5

The analysis of the cases from which the specimens were obtained at autopsy (see Table II) gives little significant data, since the cases are too few. It is worthy of note, however, that the average age at

[1] Jour. Amer. Med. Assoc., 1913, lxi, 1792-1799.

operation of these cases was practically the same in Group 3 as in the cases operated on of Group 3, while the average number of years of precedent ulcer history and the average number of months of cancer history are both shorter than the similar periods for the cases operated on of Group 3. These figures, so far as they go, would suggest that there is a small group of cases of rapidly developing cancer which symptomatically are without evidence of precedent ulcer.

TABLE III.—SUMMARY OF SUBSEQUENT HISTORIES (INQUIRIES DATED FEBRUARY 1, 1913)

GROUP 1 (?) ULCER + CARCINOMA (?)

Total cases reported	5
Alive	1
Condition good	1
Average months after operation	7
Dead	4
Under thirty days	0
Average months after operation	27.5

GROUP 1. ULCER + EARLY CARCINOMA

Total cases reported	41
Alive	23
Condition good	16
Condition fair	6
Condition bad	1
Average months after operation	30
Dead	18
Under thirty days	6
Average months after operation for remaining 12	28

GROUP 2. CANCER ON ULCER. BASE FREE

Total cases reported	94
Alive	35
Condition good	22
Condition fair	4
Condition bad	9
Average months after operation	34
Dead	59
Under thirty days	18
Average months after operation for remaining 41	14

GROUP 3. ULCER? + CARCINOMA

Total cases reported	97
Alive	19
Condition good	12
Condition fair	2
Condition bad	5
Average months after operation	24
Dead	78
Under thirty days	34
Average months after operation for remaining 44	14

The examination of Table III, which contains a summary of the subsequent histories so far as they have been obtained in these cases, shows the following:

Of the 19 patients in Group 1(?), 1 is reported in good condition seven months after operation and 4 are reported dead, an average period of twenty-seven and a half months after operation. One of these patients died of typhoid fever, the other three of cancer.

Of the 41 patients in Group 1 from whom subsequent histories have been received, 23 are reported alive; 16 of these were in good condition, 6 in fair condition, and 1 in bad condition, an average of thirty months after operation; 6 died in less than thirty days after operation, and 12 were reported dead, an average period of twenty-eight months after the operation. So far as we have been able to determine all of these patients died of cancer.

Of the 94 patients in Group 2 of whom subsequent histories have been received, 35 are reported alive, 22 in good condition, 4 in fair condition, and 9 in bad condition, an average of thirty-four months after operation; eighteen of these patients died in less than thirty days after operation and 41 more were reported dead, all except 1 apparently of recurrent cancer in an average period of fourteen months after operation.

Of the 97 patients in Group 3 of whom subsequent histories were received, 19 were reported alive, 12 in good condition, 2 in fair condition, and 5 in bad condition in an average of twenty-four months after operation; 34 died in less than thirty days after operation and 44 others were reported dead on an average of fourteen months after operation. An analytical study of the clinical data on these cases will be presented later by Drs. Graham and Eusterman.

Summary. 1. Of the 399 cases of gastric cancer from which the tissue containing the primary lesion was resected in the Mayo Clinic, 4.8 per cent. show ulcers with doubtful cancer in the border (Group 1 (?)),15.8 per cent. show ulcer with positive early cancer in the borders only of the lesion (Group 1), 36.8 per cent. show ulcers with advanced cancer (Group 2), while 42.6 per cent. of the cases show cancer in which the evidence of previous ulcer formation is doubtful (Group 3).

2. Of the 46 cases of gastric cancer from which the tissue containing the primary lesion was obtained at autopsy, 1 case (2.2 per

cent.) shows an ulcer with doubtful cancer (Group 1(?)), 7 cases (15 per cent.) show ulcer with advanced cancer (Group 2), while in 38 cases (82 per cent.) the evidence of ulcer previous to cancer formation is doubtful.

3. The clinical and pathologic data in relation to the development of gastric cancer or gastric ulcer are in close agreement: (*a*) with regard to the average age at operation; (*b*) with regard to the average period of previous history suggestive of ulcer; and (*c*) with regard to the average number of months of acute history. Such an agreement of data from two independent studies of this series of cases is not accidental.

4. It seems probably from a careful study of the clinical and pathologic evidence of this series of cases that gastric cancer rarely develops except at the site of a previous ulcerative lesion of the mucosa.

SPLENECTOMY FOR PERNICIOUS ANEMIA: REPORT OF A CASE

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In March, 1913, Eppinger and Decastello reported three cases of pernicious anemia upon which they had performed the operation of splenectomy. Other cases have since been published in Germany[1] and in one case in this country by Harpole and Fox.[2] We report the following case in order that it may assist in determining ultimately the value of the procedure:

Andrew K., aged twenty-seven years, a plumber by occupation, was first admitted to Bellevue Hospital, September 10, 1911, suffering from a high-grade anemia for which no cause could be found, but which appeared to belong in the group of simple anemias. After treatment with syrup of iodide of iron, Blaud's pill, and sodium cacodylate the patient improved to such an extent that he was discharged November 1. On June 23, 1913, the patient again entered the hospital. He had been employed as a street-car conductor, but became so weak that he was compelled to stop work. He denies syphilis.

The most essential features of the physical examination were the characteristic lemon-yellow color of the skin and scleræ; extensive pigmentation of the lower half of the abdomen with many areas of leukodermia; a number of teeth had been lost, the remaining teeth were in bad condition, and, in addition, the patient suffered from a severe type of pyorrhea alveolaris; the spleen extended three finger-breadths below the free border of the ribs and presented a hard sharp edge.

[1] For the German literature see Tuerk, Deutsch. med. Woch., 1914, xl, 371, Muehsam, loc. cit., p. 377; Discussion, loc. cit., p. 409. Also Port, Berl. klin. Woch., 1914, li, 546.

[2] Surg., Gyn., and Obst., 1914, xviii, 243.

The blood-picture on June 24 was as follows: Red cells, 1,600,000; hemoglobin, 50 per cent.; color index, 1.6; marked aniso- and poikilocytosis; slight polychromatophilia; 1 normoblast to 200 white cells; leukocytes, 6000; polymorphonuclears, 59.5 per cent.; transitionals, 3.5 per cent.; lymphocytes, 32 per cent.; large mononuclears, 3.5 per cent.; eosinophiles, 0.5 per cent.; mast cells, 1 per cent.

The Wassermann reaction was negative on June 24, 1913. The stools contained neither parasites, ova, nor blood, and later examinations were likewise negative.

During the ensuing four months, various typical symptoms of pernicious anemia were observed, such as low, continued fever, with occasional exacerbations, attacks of diarrhea, progressive weakness, increasing intensity in the coloration of the skin, and scleræ, and high pulse rate. Also, during this time, all of the better-known methods of treatment were employed; iron alone or combined with Fowler's solution, Fowler's solution or sodium cacodylate alone. Examination of the gastric contents showed a low total acidity and an absence of free hydrochloric acid, and the patient was given large amounts of this acid. The pyorrhea alveolaris was brought under control with trichloracetic acid or with iodin. In addition the patient was transfused four times by Dr. Edward Lindeman by the syringe-cannula method. The last transfusion was interrupted after 100 c.c. of the donor's blood had been injected because hemolysis was occurring. Two hours later the patient had a severe chill, the temperature rising to 103.8° F.; four hours later he passed two ounces of blood-stained urine, and at the expiration of five hours, he was sweating profusely and suffering from dyspnea.

Except for short periods, when the patient was better subjectively, his condition became progressively worse. At various times the blood gave evidence of transient attempts at regeneration, as indicated especially by an increase in the number of normoblasts, but the general tendency was toward deterioration.

July 8, examination of the blood gave the following result: Red cells, 824,000; hemoglobin, 23 per cent. (Dare); color index, 1.4, marked aniso- and poikilocytosis; slight polychromatophilia; 26 normoblasts to 100 white cells; no megaloblasts; leukocytes, 2000; polymorphonuclears, 64 per cent.; transitionals, 2 per cent.; lymphocytes, 30 per cent.; large mononuclears 3 per cent.; eosinophiles, 1 per cent.

On September 26 the blood showed: Red cells, 1,448,000; hemoglobin, 38 per cent. (Dare); color index, 1.3; moderate aniso- and poikilocytosis; no normo- or megaloblasts or polychromatophilia; leukocytes, 5000; polymorphonuclears, 47 per cent.; transitionals, 2.3 per cent.; lymphocytes, 45.3 per cent.; large mononuclears, 1.3 per cent.; eosinophiles, 2.6 per cent.; mast cells, 0.6 per cent.

About this time our attention was attracted to the case reported by Eppinger and Decastello, in which benefit appeared to have followed splenectomy, and the advisability of performing the operation upon our patient was taken under consideration. In view of the emphasis which Eppinger laid upon the urobilin content of the feces as a measure of the hemolytic activity of the spleen, Dr. John H. Richards attempted to determine this for us but was unable to find a method which was free from objection.

Since all other methods of treatment had failed to benefit the patient and the outlook appeared hopeless without operation, this was advised.

On October 27 the blood presented the following picture: Red cells 1,744,000; hemoglobin; 29 per cent. (Dare); color index, 0.8; marked aniso- and poikilocytosis; slight polychromatophilia; no normoblasts or megaloblasts; leukocytes, 2600; polymorphonuclears, 60.5 per cent.; transitionals, 1.5 per cent.; lymphocytes, 29.5 per cent.; large mononuclears, 5.5 per cent.; eosonophiles, 3 per cent.

The operation was performed October 29 under ether in the following manner: A straight incision was made through the left rectus from the last rib to below the umbilicus, and was carried through the peritoneum. The spleen was non-adherent and easily delivered without putting traction on the pedicle. Double rubber-protected clamps were placed on the pedicle and the spleen cut away. The pedicle was ligated with two double No. 3 plain catgut sutures. The abdominal wall was sutured in layers, plain catgut for the peritoneum, chromicized gut for the fascia, silkworm gut for the skin. There were no difficulties encountered in the operation and owing to the lack of adhesions the procedure was accomplished without loss of blood.

During the postoperative course the patient suffered from the fifth to the fourteenth day from very severe pains in the left upper quadrant of the abdomen. This has been noted in two other cases in which an enlarged spleen had been removed. The cause is not explained.

Dr. Richard Weil was kind enough to study the spleen for the presence of hemolysins, and has furnished the following report:

"The spleen was delivered to me immediately after operation. Two portions of the organ were at once removed and prepared for hemolytic tests

in the following manner: One portion was weighed and then thoroughly crushed in a mortar. To it were then added nine times its own weight of physiologic salt solution. The suspension was shaken for two hours in a mechanical shaker, and was then centrifuged. The supernatant fluid was used in the tests to be later described. A second portion was added to 95 per cent. alcohol in the same proportions as above described. This portion was then centrifuged and the supernatant fluid used in the hemolytic tests. A histologically normal spleen, obtained at autopsy from a cardiac case, was prepared as a control in the same fashion. The red cells were obtained from four human beings, comprising two normal individuals and two cases of pernicious anemia, one of which was the individual who supplied the spleen. These cells were washed in three changes of normal salt solution, and were then made up to a 5 per cent. suspension.

"In making the tests, 1 c.c. of each of the suspensions of red-blood cells was treated with 1 c.c. of the splenic extracts. The extracts were diluted in graded proportions for a quantitative estimation of their hemolytic activity.

"The results need not be given in detail; suffice it to say that no differences of moment could be detected between the action of the normal spleen and that of the case of pernicious anemia upon the red-blood cells."

We are indebted to Dr. E. E. Butterfield, of Dr. Norris' laboratory, for the pathological report

"Spleen measures 14 x 10 x 4.5 cm. Weight approximately 300 gms. Organ is firm; capsule is uniformly opaque. In the middle of the anterior border there is a small cyst filled with clear fluid measuring 5 mm. in diameter. Section is dark red in color. Splenic follicles are very numerous and enlarged, the largest, 1.5 to 2 mm. Otherwise the section is uniform and presents no other noteworthy gross lesions.

"*Histological Examination.* The most striking characteristic of the microscopic section is the extreme vascularity of the organ. The lymph follicles are well preserved and rather large; they consist almost exclusively of small lymphocytes; there are no germ centres. On the margin of the follicles occasional eosinophiles and large, non-granular cells are found. Central arterioles are normal in appearance. The sinuses are wide and filled chiefly with red-blood corpuscles. Numerous polymorphonuclear eosinophiles, polymorphonuclear neutrophiles, and occasional nucleated red cells are also found in the sinuses. There are numerous cellular strands running irregularly through the pulp. The strands are composed of neutrophile and eosinophile myelocytes, groups of cells of the plasma-cell type, and occasionally nucleated reds, some of which show nuclear figures.

Clusters of three or more neutrophile myelocytes with nuclear figures are also encountered in the splenic veins. Capsule and trabeculæ normal. No hemosiderosis.

"Conclusion. The cytologic details of the splenic picture are essentially those of erythrogenesis and myelogenesis. The lymphatic elements are normal or slightly hyperplastic. There is little or no regressive change and no definite evidence of blood destruction. The red-blood cells are intact and the phagocytosis of red cells encountered frequently in the spleen in other conditions is absent."

The patient's recovery from the operation was rapid. By November 3 the lemon-yellow color of the skin and scleræ had disappeared and he presented the appearance of a patient with severe secondary anemia.

November 11 the blood-examination was: Red cells, 1,605,000; hemoglobin, 31 per cent. (Sahli); color index, 1.0; marked aniso- and poikilocytosis; slight polychromatophilia; 12 normoblasts to 200 white cells; leukocytes, 4500; polymorphonuclears, 71.6 per cent.; transitionals, 2.6 per cent. On November 17 the leukocytes had risen to 12,000; they reached 16,000 on December 6, and 22,400 on January 6. Similar increases in the number of leukocytes have been reported in other cases, and Musser and Krumbhaar[1] found that it occurs after experimental splenectomy in animals.

The only other essential change in the blood-picture was observed on December 29, when, with 1,280,000 red cells and 27 per cent. hemoglobin, 51 normoblasts and 11 megaloblasts were noted in counting 200 leukocytes.

The patient improved both subjectively and objectively for a time after the operation; he grew stronger and was up in a chair for a part of each day. Later he lapsed into his former condition and, following the suggestion of Bramwell,[2] was given neosalvarsan in doses of 0.2 gm., January 13, 1914, intramuscularly, and January 20 and 29 intravenously. As the patient continued to grow weaker the last two doses of the series were not administered.

On January 13 before the administration of the neosalvarsan, the blood-examination was as follows: red cells, 1,760,000; hemoglobin, 25 per cent. (Dare); color index, 1.4; marked aniso- and poikilocytosis; slight polychromatophilia; 18 normoblasts and 8 megaloblasts to 200 leukocytes; leukocytes 14,200; polymorphonuclears, 49 per cent.; transitionals, 7 per cent.; lymphocytes, 36 per cent.; large mononuclears 7 per cent.; eosinophiles, 1 per cent.

February 25, examination of the blood gave the following result: Red cells,

[1] Journ. Exp. Med., 1913, xviii, 487.
[2] Brit. Med. Jour., 1913, i, 1093 and 1256.

1,264,000; hemoglobin, 18 per cent. (Dare); color index, 0.7; aniso- and poikilocytosis and polychromatophilia marked; 111 normoblasts and 16 megaloblasts in 200 white cells; leukocytes, 17,450; polymorphonuclears, 46 per cent.; lymphocytes, 44 per cent.; large mononuclears, 8 per cent.; eosinophiles, 1 per cent.; mast cells, 1 per cent.

The use of the neosalvarsan makes it impossible, of course, to draw any conclusion as to the effects of the splenectomy except in the interval before its administration. In this interval there was no evidence of more than temporary improvement, as has previously been stated.

At the present time, April 24, six months after the operation, the patient, while looking better and feeling better, is just beginning to sit up. The blood examination is as follows: Red cells, 1,060,000; hemoglobin, 22 per cent. (Dare); color index, 1+; marked aniso- and poikilocytosis; slight polychromatophilia; 52 normoblasts and 3 megaloblasts to 200 white cells; leukocytes 18,400; polymorphonuclears, 45.5 per cent.; transitionals, 3 per cent.; lymphocytes, 32 per cent.; large mononuclears, 10 per cent; eosinophiles, 9.5 per cent.

STUDIES IN PERNICIOUS ANEMIA

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In the past few years the interest of pathologists and clinicians has been attracted strongly to the group of hemolytic anemias. Recently through the courtesy of Doctor Hans Eppinger and Doctor A. von Decastello, of Vienna, it was my privilege to see a number of cases of hemolytic spenonomegaly and of pernicious anemia, and to study sections of the spleens removed at operation. I have been able to collect thirty-one cases of splenectomy in pernicious anemia, either directly reported or mentioned in discussions on papers read. To these may be added one which Doctor Judell, of San Francisco, has kindly allowed me to report, and one operated upon in my service at the University of California Hospital.

The operation originated in the minds of the two Vienna clinicians independently, both of whom sent cases to operation in March, 1913. Doctor Eppinger's work on the liver and spleen is well known. He is a most enthusiastic believer in the important role of the spleen in the production of hemolytic anemia and hemolytic icterus. He has advocated and has had carried out by Ranzi and Exner splenectomy for the relief of Banti's disease, Hanot's cirrhosis, congenital and acquired hemolytic icterus, splenic vein thrombosis, chronic and acute icterus of uncertain origin, and, lastly, pernicious anemia. He has emphasized in several papers the importance of urobilin in the urine and stools as a measure of pathological hemolysis, and with Charnas has elaborated a method of urobilinogen determination in stools. He has pointed out that the iodin content of blood after removal of cholesterin and cholesterin esters runs fairly parallel to the degree of pathological hemolysis in the body. He has

dwelt upon the similarity of the histological picture in spleens from hemolytic icterus and pernicious anemia, and he proposed splenectomy in pernicious anemia largely because of the operative results in congenital and acquired hemolytic icterus, reported by Banti, Micheli, Kahn, Chauffard, and others. He reports five cases from a few days to three, four, seven, and nine months after operation. In all five patients pathological hemolysis was shown by the icteric coloring and large amounts of urobilinogen in the stools. The operation put an end to the increased blood-destruction, and, though Eppinger does not believe that the seat of the disease is in the spleen, he is convinced that "hypersplenism" is an important factor. Three of his patients have returned to business and another is decidedly better than before the operation. A man operated upon in March I saw in September, 1913. He had gained thirty-six kilograms since the operation and was at business, but his color was not normal and the blood was still of the megalocytic type.

G. Klemperer and Hirschfeld have reported eleven cases operated upon by Mühsam. Three patients died as a direct result of the operation and two shortly afterward. Many cases were in a desperate condition when sent to the surgeon. Here, as in other reports, one is impressed with the temerity of the clinician who refers, for operation, patients with blood-counts of 500,000 to 700,000 and hemoglobin estimations of 10 to 15 per cent. Klemperer had long thought of splenectomy in pernicious anemia for other reasons than those of Eppinger. The first suggestion came from a case of Banti, with marked secondary anemia, that was operated upon by Mühsam and returned after one and a half years with polycythemia. Several instances of polycythemia after removal of the normal spleen or the diseased spleen in Banti's disease are cited from the literature. The theory is advanced of some normal regulating function of the spleen upon the activity of the bone marrow; after removal of the spleen, particularly when diseased, this inhibition is released and normal and abnormal erythrocytes are thrown rapidly into the circulation. In nine cases there were great numbers of normoblasts and erythrocytes with Howell-Jolly bodies in the peripheral blood. In one case seven months after operation megalocytes were prominent in the blood-picture, and there was no diffi-

culty in recognizing the pernicious type. The authors agree that splenectomy may bring about remissions when other means have failed, but Hirschfeld states plainly "Die Splenektomie bei der perniziösen Anaemie ist nur eine symptomatische palliative Therapie."

Von Decastello was influenced in his advocacy of operation by the results obtained by Banti, Micheli, and Antonelli with splenectomy in hemolytic icterus and hemolytic anemia. He reports 6 cases, in 2 of which death followed immediately upon the operation. In a woman, nine months after operation, who improved greatly in strength and for a time in the blood-picture as well, the blood is again slowly changing to the abnormal megalocytic type with high color index. In a second patient the same return of megalocytosis was observed after an initial rapid improvement. In a third case the glossitis described by Hunter first appeared after operation and the blood-picture changed very slowly, and only after four weeks' treatment with arsenic. In a fourth instance improvement was rapid, and six months after operation the blood-count is 4,000,000, with practically normal erythrocytes. Von Decastello notes particularly the cessation of stomach symptoms and the disappearance of profound weakness almost immediately after operation. He records also the persistence of achylia. He assigns some of the benefit after splenectomy to the increased activity of the bone marrow, and he concludes that in all probability splenectomy will only lead to remissions and not to cure.

Port noted the rapid disappearance of urobilin from the urine after operation and the usual increase of normoblasts and Howell-Jolly bodies. He could demonstrate no hemolysins from alcohol and ether extraction of the spleen. Huber's patient, a woman, was not benefited by splenectomy; in fact the blood changed for the worse and large amounts of urobilinogen were still present in the stools. Mosse reports the apparent cure of a woman aged thirty-eight years, four months after operation. The blood-picture is now normal; before the operation it showed 1,100,000 erythrocytes, 3000 leukocytes, and 30 per cent. hemoglobin. He mentions also a case of hemachromatosis, which he includes among the hemolytic anemias, as much benefited after splenectomy.

Türck in his interesting paper, "Die Bedeutung der Milz bei anemischen Zuständen in Bezug auf Pathogenese und Therapie,"[1] mentions a case three months after splenectomy. The blood-changes were still unmistakably those of pernicious anemia, glossitis and stomatitis had returned worse than before the operation, but had yielded again to arsenical treatment. Pappenheim in the discussion following Türck's paper mentions a case in the Kraus Clinic, Berlin, operated upon three and a half weeks before. The general condition and the blood-picture were both worse, despite the appearance of many Howell-Jolly bodies and other regenerative signs. Roemer[2] mentions a patient, a woman, aged fifty-five years, whose blood was once brought nearly to normal by arsenical treatment. She was operated upon during an exacerbation when treatment had failed to give any bone-marrow reaction and with a blood-count of 500,000 and hemoglobin 10 per cent. A tremendous reaction followed operation, with disappearance of poikilocytosis and a rise in count to 1,500,000 and hemoglobin 35 per cent. Improvement continued for four weeks, but was followed by a relapse in the last two weeks. A second case, operated upon fourteen days before, showed improvement, but Roemer is certain that this will not continue.

Harpole and Fox report remarkable improvement in a case sent to operation on account of the failure of other methods of treatment and of the enlarged spleen. There was the usual postoperative normoblastic crisis. They had not heard of the Vienna cases at the time. Von Decastello mentions a verbal report of von Jagic without giving any details of the operated case.

Doctor Judell's patient, a woman, aged fifty-two years, had been ill two years. Mental confusion and vomiting had been prominent symptoms. Splenectomy was done February 23, 1914, largely under local anesthesia, with small amounts of gas and ether. The blood-count the day of operation showed 2,860,000 red cells and 5160 leukocytes. Immediately after the operation vomiting and abdominal distress ceased. The mental symptoms have grown worse. April 19, 1914, the blood-count was 3,050,000 red cells, 7600 leukocytes, with 31 per cent. polynuclear neutrophiles, 66 per

[1] Deutsch. med. Woch., February 19, 1914.
[2] Aerztlicher Verein zu Hamburg, February 17, 1914.

cent. lymphocytes, 2 per cent. large mononuclear forms, and 1 per cent. basophiles; 7 normoblasts and 4 megaloblasts were seen during the differential count. In this case there was no active hemolysis before operation, as evidenced by urobilin in urine or stool, and the subsequent marrow reaction was slight, comparatively few normoblasts appeared in the blood, and there were practically no Howell-Jolly bodies.

A man, aged sixty-one years, a native of Sweden, was examined a number of times at the University Hospital from April, 1913, to January 26, 1914. He had been weak and unable to work for five years before his first hospital entrance, and probably in those years had had at least two remissions of the disease. There had been moderate nausea and vomiting at different times, and recently some dull, dragging pain in the left hypochondrium. For a month tingling had been felt in the fingers and toes. The yellowish color of his face had been noticed only recently. Sexual power had been absent for four years. The spleen at first was large by percussion and later was plainly felt. A note was made April 15, 1913: "His color suggests a combination of pernicious anemia and chronic heart disease. The sparse hair, thick features, large hands, with chronic joint changes, the small thyroid, the history of impotence suggest a polyglandular syndrome." Achylia was determined on several occasions. The Wassermann, luetin, and von Pirquet tests were negative. Urobilin was increased in the urine and urobilinogen in the stools. The stools were negative for parasites. Glossitis was never present. From May to December, 1913, the patient was at home gradually growing weaker, though there was a slight remission in September. Paresthesia had risen from the feet to the level of the umbilicus and from the hands to the elbows. As there had been no improvement in symptoms or in the blood-picture under treatment with arsenic the patient was referred January 13, 1914, to the surgical service for splenectomy. Urobilin in the urine at this time was moderately increased, urobilinogen in the stools slightly so. Splenectomy was performed January 15 by Doctor W. I. Terry under gas and oxygen and ether anesthesia. The spleen was bound by adhesions to the diaphragm, stomach, and at the lower pole to the omentum. It was freed with difficulty,

Date 1913	Hgb. %	Reds per c.mm.	Whites per c.mm.	Neutro. %	L. mono. %	Lympho. %	Eosino. %	Mast. %	Normoblast per c.mm.	Platelets per c.mm.	Remarks.
Apr. 15	45	2,228,000	4,000	65.6	5.6	26.8	1.6	0.4	...	About normal.	Reds well colored. Average size larger than normal. Moderate poikilocytosis and anisocytosis. Moderate stippling and polychromatophilia. Blood-serum negative for urobilin. Doubtfully positive test for bilirubin by Gmelin.
Apr. 23	45	2,084,000	4,800	48.8	9.2	40.0	1.2	0.8	Rare.	....	Reds as before.
Apr. 29	50	2,184,000	3,900	61.6	12.0	24.6	1.4	0.4	...	....	Polychromatophilia more marked.
May 5	50	2,996,000	4,200	57.2	8.4	30.0	4.0	0.4	Very rare.		
Dec. 20	40	2,406,000	5,400	53.4	12.8	27.8	5.8	0.2	Rare.	Diminished.	Average size of red cells = 9.09. Staining reactions as above. Fragility = beginning hemolysis at 0.48 per cent. NaCl—complete hemolysis at 0.30 per cent. NaCl.
1914 Jan. 7	35	2,841,000	7,100	66.6	9.4	22.0	1.8	0.2	...	97,000	Reds as above. Reticulated red cells = 0.6 per cent.
Jan. 13	40	2,936,000	4,800	66.0	10.0	20.5	1.5	2.0			
Jan. 15	Splenectomy										
Jan. 16	35	2,980,000	12,300	84.0	5.0	11.0	...	...	1,100	....	Marked polychromatophilia and stippling. Moderate numbers of Howell-Jolly bodies.
Jan. 17	30	2,732,000	7,000	88.0	5.0	7.0	...	...	950	....	Marked polychromatophilia and stippling. Moderate numbers of Howell-Jolly bodies.
Jan. 19	40	2,900,000	6,700	54.5	17.0	28.5	...	...	2,100	176,000	Numerous Howell-Jolly bodies. Reticulated red cells = 4.1%
Jan. 20	40	2,784,000	6,400	73.0	12.0	15.0	...	...	2,800	....	Reds as before. Howell-Jolly bodies still numerous.
Jan. 23	37	2,656,000	7,800	69.0	7.0	24.0	...	...	930	....	Reds as before. Howell-Jolly bodies still numerous.
Jan. 24	40	2,736,000	8,200	63.5	8.0	28.0	0.5	...	2,000	....	Fewer changes in red cells. Howell-Jolly bodies rare.
Jan. 26	40	2,984,000	8,400	76.5	10.0	13.5	...	...	1,400	....	Fewer changes in red cells. Howell-Jolly bodies rare.
Jan. 26	Died.										

the operation lasting one hour and forty minutes. The splenic artery was tied before the splenic vein. The weight of the organ was 390 grams. After operation there was marked meteorism and considerable cough. Bronchopneumonia developed in the left lower lobe, gradually progressed, and the patient died January 26 from bronchopneumonia, thirteen days after operation. There was a recent vegetative endocarditis of the aortic valves. There was no increase of hemolymph glands, while the marrow of the long bones could not be examined. Despite the postoperative infection there was well-marked evidence of an active bone-marrow reaction. Urobilin was not present in the urine after operation. Urobilinogen in the stools was moderately increased January 18, 19, 21, and 23.

Of the 33 cases of splenectomy for pernicious anemia recorded above, 8 died immediately or not long after the operation. There can be no question that in a number of instances rapid improvement followed the surgical procedure. A few patients have regained strength so rapidly—long before the blood-count has risen much—as to confirm the opinion of Banti that poisons from the spleen act at times hyposthenically. A patient of Eppinger's gained greatly in weight. Von Decastello and Doctor Judell have noted the improvement in appetite and the disappearance of stomach symptoms. The achylia persisted in von Decastello's cases. In nearly all instances reported the pathological hyperhemolysis was controlled by splenectomy. The icteric coloring, if present, disappeared, the liver became smaller, urobilinuria ceased in a few days up to two or three weeks, and urobilinogen in the stools was no longer excessive. In the case of Huber, however, urobilinogen was still present in large amounts in the stools three months after operation. In a case of Eppinger's urobilinuria persisted and urobilinogen in the stools was still increased. My patient noted the complete disappearance of the characteristic paresthesia that had been so annoying before operation. Chief interest centres in the remarkable changes in the blood-picture almost immediately after operation, the characteristic feature being the appearance of great numbers of normoblasts, reticulated erythrocytes, and erythrocytes with Howell-Jolly bodies. There can be little question that there is an active marrow reaction. Klemperer speaks of the removal of a hormone that normally inhibits

bone-marrow activity; he regards the long persistence of normoblasts and Howell-Jolly bodies after splenectomy in pernicious anemia as evidence of the persistence of some abnormal marrow irritation. Von Decastello suggests that perhaps the marrow reaction is due to the irritation of some abnormal constituents of erythrocytes that have been deprived of the usual modifying influence of the spleen; the remarkable rise in hemoglobin observed in a few instances may indicate an unusual amount of readily elaborated material in liver and marrow. Von Decastello remarks upon the analogy of the blood-changes after splenectomy with those seen occasionally after small blood-transfusions. We have seen above that at times the removal of a normal spleen may be followed by polycythemia, an evidence of hyperactivity of the bone marrow. The normoblastic and Howell-Jolly body crises after splenectomy for other conditions than pernicious anemia are, however, by no means so marked. Howell-Jolly bodies do not appear after splenectomy in rabbits or mice, but may be observed in great numbers after the operation in rats. Von Decastello and Biedl have seen them after splenectomy in normal dogs. It is interesting to note the constancy of their occurrence in the blood from cases of hemolytic icterus. Schur found them very plentiful in a case of pernicious anemia which at autopsy showed a markedly atrophic and fibrous spleen. The great numbers of normoblasts persist usually for two or three weeks, rarely longer; the nuclei may either be normal or irregular and fragmented. The Howell-Jolly bodies have been much increased as late as seven months after operation; they may occur without much or even any improvement in the general blood-picture. At times there is a quick rise in the number of erythrocytes, 1,000,000 within a week. There may be rapid improvement in anisocytosis, poikilocytosis, and the number of megaloblasts, and the color index may quickly fall. Megalocytes disappear more slowly and the characteristic megalocytic type of blood may be found months after operation when the patient feels quite well or, after initial improvement or even disappearance, the megalocytic picture may be reëstablished. Occasionally the red-cell count increases very slowly while the percentage of hemoglobin steadily rises. Von Decastello notes the unusual count of 1,710,000 ery-

throcytes, 4560 leukocytes, 70 per cent. hemoglobin, and a color index of 2. The leukocytes may or may not increase after operation; usually they do, as after splenectomies in animals. Both Klemperer and v. Decastello mention the polymorphism of the neutrophilic nuclei. This is a common feature of pernicious anemia, but not often described. Doctor Briggs at the University Hospital has in 10 out of 12 cases found a marked increase in the number of lobes of the nuclei of the neutrophiles, often five to eight—a shift to the right in the terms of Arneth. In 8 cases of severe secondary anemia the number of lobes in the nuclei were either normal or diminished. Usually the blood-plates in pernicious anemia are decidedly diminished, after splenectomy they may be much increased, and at times may form a striking feature of the blood-slide. Fragility of the erythrocytes has been measured in a few cases. In Mosse's case there was decreased resistance to salt solutions, in von Decastello's cases and in a case of mine the limits were essentially normal. Splenectomy does not here seem to increase the resistance of the red cells as it does experimentally, and the decreased hemolysis after operation cannot be referred therefore to the production of hardier generations of erythrocytes.

Clinically in pernicious anemia the spleen is reported usually as not enlarged. Cabot records enlargement in 13 of 110 cases, Billings in 5 of 20 cases, McCrae in 6 of 40, from the Johns Hopkins material. Lyon, in his article in Osler's system, mentions three cases in which a diagnosis of splenic anemia had been made on account of the great size of the spleen. Hunter records autopsy weights of 570, 330, 300, 390 grams. If the weight of the normal spleen be placed at 150 to 200 grams the organs removed at operation are most often increased in size; 570 (Mosse), 432 (Port), 500, 350, 350, 286, 435 (v. Decastello), 390 (Moffitt).

The spleen is usually described as markedly hyperemic even though the splenic artery has been ligated before the veins; occasionally it may be small, hard, and fibrous. I have had an opportunity of studying sections of the spleen from eight operated cases. The striking thing, as emphasized by all reporters, is the hyperemia of the pulp, the sinuses being comparatively thin and empty. This pulp hyperemia is tremendously marked in the case of Doctor Judell

and least marked in my own. The capsule and trabeculæ are usually little changed. The follicles may be somewhat atrophied or normal or decidedly increased, as in cases of v. Decastello and in my own. The arteries of the hilus may be sclerotic, tortuous, and even aneurysmal. Eppinger has laid great stress upon certain changes of the smaller arteries which he regards as constant and characteristic. These changes are well illustrated in the following preparations: The walls of the follicular arteries are thickened and the lumen often encroached upon by hyaline masses. The pulp capillaries are also thickened. It is difficult to believe with Eppinger, however, that these vascular changes can divert the normal blood-flow from the pulp and Seidel capillaries to the sinuses and turn it through the intrafollicular capillaries into the interstices of the pulp. As Türck pertinently observes, if the vascular changes were the cause of the pathologically increased hemolysis it is difficult to see how remissions could occur. Occasionally macrophagocytes appear definitely increased and erythrocytes and fragments of erythrocytes can be seen within them. Polynuclear neutrophiles can be found in every section, eosinophiles are occasionally seen in considerable numbers, and myelocytes more rarely. In 1 case there were numerous small foci of this myeloid metaplasia. Pigment varies greatly. In 2 cases there was practically none; in 2 there was a small amount of finely granular intracellular pigment, and in 4 there were great quantities of coarse brownish granules in and between the cells of follicles and pulp. The hyperemia of the pulp and the thickened arteries seem to be the constant histological findings, but even these vary considerably in different sections. There is certainly no indication of a greatly increased phagocytic function in any of the preparations.

It is difficult to define the results of splenectomy in pernicious anemia. The removal of spleens with exactly the same histological appearance in cases of congenital hemolytic icterus has led to permanent cure of the disease. In certain cases of pernicious anemia no benefit has been obtained, in others striking improvement has resulted, and cases are reported apparently cured after periods of three to nine months (Mosse, Eppinger); in still others great betterment in symptoms and blood-pictures has been followed after weeks

or months by a relapse. In a few instances threatening exacerbations have been apparently checked by the administration of arsenic. The varying degrees of reaction to the operation must depend upon the condition of other organs, particularly liver, bone marrow, and lymph glands. The role of the spleen in the disease may be compared in part to the role of the thyroid in exophthalmic goitre. Very probably the condition of "hypersplenism" of which Eppinger speaks is brought about by poisons reaching the spleen in the arterial circulation. As in Banti's disease, erythrolysis does not take place in the spleen, but the corpuscles are in some way sensitized and then destroyed in liver, marrow, and lymph glands. The Kupffer cells of the liver have been found in a state of increased phagocytosis of erythrocytes in cases of pernicious anemia, and a number of authors, particularly Warthin, Weigert, and Eppinger, have emphasized the importance and increased activity of the hemolymph glands. After splenectomy in animals large numbers of cells containing erythrocytes are found in the sinuses of lymph glands. Pearce and Austin have noted an increase of endothelial cells in liver capillaries and lymph glands after splenectomy in dogs; these cells become phagocytes of red cells after injection of hemolytic sera and compensate for the erythrocytolysis in the spleen. Pappenheim considers the milk spots of the omentum as rudimentary hematopoietic tissue and thinks they form the "anlage" of multiple splenoid tumors developing after splenectomy which may assume hemolytic functions. Eppinger is inclined to refer relapses after operation to the increased hemolysis occurring in hemolymph glands. He suggests arsenic to check their development, and dwells upon the necessity of early operation in pernicious anemia before other hemolytic organs than the spleen have been involved.

Though since the early work of William Hunter we admit the great importance of the hemolytic function of the spleen, I think we must, with Warthin, realize that the infective agent or toxin of pernicious anemia "may act differently at different times or that there may be several hemolytic poisons, and that there may be splenic, lymphatic, hemolymphatic, or marrow hemolysis." The shifting clinical pictures, the varying reaction at different times to remedial measures, like arsenic, blood-transfusion, thorium X, salvarsan,

splenectomy, the marked hemolysis in some cases (urobilinuria, icterus) and its absence in others, the inconstancy of marrow reactions, all speak for a widespread influence of the poison in the economy with maximum effects apparent now in this organ, now in the other.

The importance of the bone-marrow reaction has long been known to clinicians, and is again emphasized by the above-described blood-changes after splenectomy. Few conditions apart from pernicious anemia are marked by a megalocytic type of blood. In the acquired form of hemolytic icterus the anemia may be extreme. The cases reported by Banti in 1911 and Antonelli in 1912, apparently cured by splenectomy, resembled pernicious anemia very closely. A case recently reported by Giffen from the Mayo clinic "suggests the diagnosis of an atypical pernicious anemia." A few normoblasts and megaloblasts were found in the blood, and after splenectomy "a shower of normoblasts and megaloblasts occurred." The spleen weighed 1640 grams. The fact that the patient is living two and a half years after operation, though weak and anemic, speaks much in favor of a hemolytic anemia other than pernicious. Cases similar to this and Antonelli's have been reported by Parkes-Weber, v. Decastello, Chauffard and Troisier, Gilbert, Chabrol and Bernard. Nearly always in this group the spleen is much larger than in pernicious anemia, and the corpuscular fragility is more frequently increased. Undoubtedly the chief hemolytic agent in this group is the spleen, and its removal may permanently put an end to the disease. Perhaps, as Banti and Warthin first suggested and as Eppinger now affirms, there may be some cases of pernicious anemia in which the hemolytic activity of the spleen overshadows other lesions, and perhaps in these splenectomy may as in other hemolytic anemias lead to permanent improvement or even cure. But the proof of this theory is still inconclusive despite the benefit reported from operation. We still feel that the secondary hemolytic organs, liver, lymph glands, and particularly bone marrow, are involved in the disease as well as the spleen. The changes in the blood after operation suggest, it is true, the removal of some inhibitory influence on the marrow, but that the medullary reaction is a most unusual one is shown by the tremendous numbers of normoblasts and Howell-Jolly bodies.

We have in the operation, as Klemperer and von Decastello point out, a means of bringing about a remission fairly certain when other means have failed. But, as every clinician who has seen many cases of pernicious anemia well knows, it is impossible to say that a patient is in a condition so desperate that no remission can again occur. I have seen a man in coma for three days with hemorrhages from gums, nose, and rectal mucous membranes, a blood-count of 600,000, and have seen this same man back at work for a year after the remission that followed directly this desperate situation. Quincke's case with 143,000 erythrocytes recovered from this exacerbation. Hirschfeld followed a case from 1894 to 1907, death occurring in the ninth relapse. William Hunter demonstrated a patient last summer in London who was still at work thirteen years after the disease was first discovered. Pearce, Krumbhaar, and Musser have demonstrated experimentally the slower blood regeneration in splenectomized dogs. Smaller losses of blood cause a graver anemia in these than in normal dogs and shortly after injection of hemolytic sera their erythrocytes become less resistant and remain so longer than in normal animals. Port in dealing with the various classes of hemolytic poisons notes that the absence of the spleen is an important factor in causing a persisting corpuscular fragility after injection of hemolytic sera. The absence of the spleen is an important factor in increasing the severity of anemia and in delaying the process of repair.

There are many reasons, therefore, for weighing carefully the question of splenectomy in a given case of pernicious anemia. Eight of thirty-three cases died immediately or soon after the operation. Thrombophlebitis, bronchopneumonia, mental symptoms have been complications in other instances. The patients of Pappenheim, Huber, Roemer were worse or little benefited. In two of v. Decastello's cases initial improvement is being followed by relapse.

Certain passages may be quoted from Banti's discussion on the "Clinical Aspects of Hemolysis:" "The spleen (as for that matter, the other organs also) has not an autochthonous and primitive hemolytic function: it responds in a secondary manner to the agents which do not reside within it. . . . Splenectomy does not, therefore, eradicate the disease—that is, the agents of the disease,

whose nature and seat remain entirely unknown to us—but eradicates rather the principal instrument, by means of which these agents become pathogenic." We are yet ignorant of the unknown agents which are brought to the spleen and marrow by the circulation and which are the ultimate cause of the disease pernicious anemia. I have in a previous paper mentioned the similarity of the infective pernicious anemia of horses with the disease in man. I have since had opportunity of examining sections from liver and spleen in equine anemia and of observing changes similar to those in human cases. Mack has described hyperemia of the spleen, increase of pigment, in one case marked thickening of the arteries. Erich Meyer and his assistant Seyderhelen have noted the similarity of both blood-picture and histological changes in equine and human cases. Matthes in an article on *Die Hunterische Glossitis bei perniziöser Anemie* emphasizes the infectious nature of the disease and has observed the occurrence of several cases in one family more than once; in one family three members were affected. His assistant, Hurter, tried inoculations into monkeys with negative results. Since my last report another horse has been injected with blood from a patient with severe pernicious anemia but with negative result. On January 15, 40 c.c. of an emulsion in salt solution of the spleen just removed from a man with pernicious anemia was injected subcutaneously into a third horse. Neither temperature nor blood-counts have changed since then up to May 1. Owing to the difficulty of the operation in horses it seems impossible to try the effect of splenectomy in animals in an active stage of the infection.

DISCUSSION ON THE PAPERS OF DRS. COLEMAN AND HARTWELL, AND MOFFITT

Dr. W. S. Thayer: I have had experience in the removal of the spleen in pernicious anemia in two cases. The observations of Eppinger, King, and others have been interesting and suggestive. The results of splenectomy in those instances of splenomegaly associated with repeated gastric hemorrhages have in my experience been exceedingly good. Moreover, splenectomy today may be done with relative impunity even in the gravest anemias

in association with direct transfusion. Indeed, a year ago Dr. Finney operated on a case of primary splenomegaly with hematemesis in a boy of about eight years who was really *in extremis*. The operation was performed under transfusion and at the end of the operation he was in better condition than he had been for some months. In view of these circumstances I was led to advise the performance of splenectomy in an instance of probable pernicious anemia last November.

The patient was a woman, aged forty years, who in the winter of 1912, following an attack of diarrhea, began to suffer from paresthesia of the legs; a month or so later she was found to be anemic. The anemia increased steadily and in the early fall with a hemoglobin under 30 per cent., a direct transfusion was performed. The hemoglobin rose to 50 per cent., the general condition improved and what is unusual in true Addisonian anemia, she held her gain following transfusion for a month or two, but by February when I first saw her she had lost ground considerably, the blood-count showing: Red-blood cells, 2,714,000; white-blood cells, 5600; hemoglobin, 45 per cent.

The appearance of the blood was very suggestive of pernicious anemia. There was no great poikilocytosis but there was very marked anisocytosis and a rather large percentage of small mononuclear leukocytes; nucleated reds were not seen with the exception of one suspicious megaloblast. The spleen was palpable, coming several finger-breadths below the costal margin on inspiration. The reflexes in the legs were considerably increased. In March, 1913, there was a second transfusion followed by a long period of treatment with rest and arsenic in a hospital; during this period she improved, but in the early fall the anemia began to increase again, and anisocytosis became more marked, the color index was rather high and the general appearance of the condition was that of a pernicious anemia. The paresthesia in the extremities increased and there were slight objective sensory disturbances; there was an ankle clonus and well-marked Babinski reflex on both sides. The operation was performed in the middle of November when the blood-count was: Red-blood cells, 1,500,000; white-blood cells, 5000; hemoglobin, 28 per cent.

She was transfused at the time of the operation which was performed under general anesthesia. At the end of the operation which was well borne, the hemoglobin was about 45 per cent. Since this time the patient has improved rapidly and without interruption, and now, six months after the operation, she seems quite well. The last blood-examination made toward the end of March showed: Red-blood cells, 4,900,000; white-blood cells, 7500; hemoglobin, 82 per cent.

In the early part of April the hemoglobin was 87 per cent. and the microscopic appearance of the blood showed no abnormalities. The patient is up and about, but shows a well marked spasticity of the lower extremities.

In the second case, a colored woman, the operation was performed in

February after several months without noticeable improvement in the hospital. This was a typical instance of yellow Addisonian anemia. The last blood-count three days before the operation on February 3d was: Red-blood cells, 1,752,000; white-blood cells, 3680; hemoglobin, 27 per cent.

Transfusion was performed immediately after the operation. The patient improved slowly but steadily, but this improvement came to a standstill about a month ago when the blood-count was about 3,500,000. While the patient is in fairly good condition the blood still shows slight poikilocytosis and the general aspect of the patient is rather that of a pernicious anemia. Indeed, within the last month the blood-count has dropped slightly.

It seemed to me worth while in connection with the reports which we have heard, to mention these two cases which I have intended to report later. The first patient appears to be well, though there are well marked spinal scleroses. The condition of the second patient cannot be said at the moment to differ in its general aspect from that of many instances of pernicious anemia during a period of remission. The only essential difference is that the leukocytes in the last several counts have amounted to about 10,000.

The question must be asked as to whether the first instance was a typical pernicious anemia. The absence of a marked poikilocytosis and the circumstance that the patient never showed the yellow color so common in pernicious anemia as well as the absence of megaloblasts in the blood might lead one to fancy that it was not a typical Addisonian anemia, but before operation no nucleated reds whatever were found in the blood and in other respects the appearance and behavior of the case was quite characteristic of a progressive pernicious anemia. It is obviously impossible at this time to express an opinion as to the future course of these cases. I rather expect from the appearance at the moment that the second instance will show a relapse.

Dr. Joseph L. Miller: This is an important subject for the reason that in the next year or so a great many patients with pernicious anemia are going to lose their spleens.

The removal of the spleen has undoubtedly some effect upon the blood. It stimulates the bone marrow to new blood-formation, and definitely raises the resistance of the red-blood corpuscle which has a bearing on hemolysis. We know that following the removal of the spleen in these cases of pernicious anemia there is in many instances evidence of marked increase in blood-formation. We also know there is evidence of markedly diminished blood-destruction. For instance, Eppinger has determined the amount of urobilin in the stools, using that as an index of blood-destruction. He has found that in cases of pernicious anemia the amount of urobilin in the stool is greatly increased, but after the removal of the spleen the

amount of urobilin drops down to normal, showing that increased blood-destruction apparently stops after the spleen is removed. To my mind a ready explanation of the improvement after the removal of the spleen is that the resistance of the blood-corpuscle is increased, so that the hemolytic agent present is no longer able to destroy the more resistant red corpuscle, but the hemolytic agent itself is not affected by removal of the spleen.

I recall one case of pernicious anemia in which, after the spleen was removed, there was a marked improvement in the patient's blood-picture. After a few months it was practically normal. At the time the patient had the spleen removed there were slight evidences of cord changes, but since then the cord changes have become much more marked, showing that at least the agent responsible for cord changes, and not unlikely this is the same agent that caused the blood-hemolysis, persisted after removal of the spleen.

Dr. E. Libman: I think it is well worth while in every case of pernicious anemia to try transfusion using a large amount of blood, applying either direct transfusion or the indirect method of Lindemann. The results which I have seen up to the present time are at least as good as those which have been described as occurring after splenectomy. In one case that has been studied for almost two years the patient's hemoglobin was originally at 18 per cent. It was raised to 60 per cent. after the first transfusion, and after a short time it rose to 100 per cent., and the patient remained practically well for a year. Shortly after that a second transfusion was done, but in the last two months the hemoglobin dropped again and a splenectomy has been performed.

The question of cord changes in pernicious anemia is a very interesting one. Dr. Moffitt stated that the paresthesias in this case disappeared after splenectomy, whereas in Dr. Thayer's case they did not.

I had recently under observation a man who came to me with a hemoglobin of 80 per cent. He had evidences of changes in the cord which were suspected of being due to pernicious anemia because of the tendency to macrocytosis in the blood. The patient's physician, his son, stated that the father had never looked anemic. The hemoglobin dropped after one year to 20 per cent., and the typical evidences of pernicious anemia were absent. After transfusion, although the hemoglobin was considerably raised, the spinal cord symptoms remained unchanged. This made it appear very probable to me that in all probability the spinal cord changes are due to the agent which caused the blood-changes and not due to the anemia.

Dr. R. M. Pearce: It is not always possible to correlate experimental evidence with clinical observation, and this is especially true of work on the spleen. With my assistants I have been interested in the study of the

spleen for a period of several years, particularly with reference to the results of experimental extirpation of the organ in the dog, and since there is an increased tendency for surgeons to remove the spleen in pernicious anemia, I have tried to analyze the clinical results of this procedure in the light of our experimental findings. The results are not satisfactory. In the first place, we find that after removal of the spleen of a normal animal, there is always a tendency to anemia lasting sometimes several weeks. After the animal has recovered from this anemia, if blood-destruction is caused by hemolytic agents, the reparative process is much slower than in normal dogs receiving the same hemolytic agent. Also we cannot demonstrate that the spleen has a definite relation to the iron metabolism, as has been claimed by Ascher and his pupils. A number of animals have been studied by us for long periods of time, but we have found it quite impossible, by direct estimation of the iron of the feces, to determine that iron elimination is altered in the absence of the spleen.

Dr. Miller has brought up an important point concerning the increased resistance of the red cells after splenectomy. In our work we have found this to be a very definite and constant result of splenectomy. It is possible this phenomenon may explain the improvement seen clinically after operation; and it may be that after a time this increased resistance is overcome by the hemolytic agent responsible for the anemia, thus explaining the return of severe anemia which so frequently follows the temporary improvement. Another improvement point mentioned by Dr. Miller, is that of changes in the bone marrow. In our experimental work no changes in the bone marrow were seen in the early anemic period. Two or three months or more may elapse without changes in the bone marrow, but after six months one nearly always finds a transformation of the fatty marrow to red marrow. This change, however, comes altogether too late, in the dog at least, to explain the temporary improvement which follows splenectomy. It may be different in man. We are inclined to feel that the problem is so complicated that it can only be worked out experimentally on the basis of distinct unit problems. In the matter of blood-destruction and regeneration, the bone marrow, spleen, lymph nodes and the liver are concerned. Sometimes one, sometimes several of these tissues are at fault. Sometimes there is compensation, while at other times there is none. Until we have a more intimate knowledge of the various interactions and compensations in blood-destruction and regeneration it will be impossible to predict the results of splenectomy. That it is of value in certain forms of splenomegaly there can be no doubt; in pernicious anemia it would appear, however, to be a last resort when all other treatment fails and the outcome is hopeless.

BOTULISM: A REPORT OF FOOD POISONING APPARENTLY DUE TO EATING OF CANNED STRING BEANS, WITH PATHOLOGICAL REPORT OF A FATAL CASE[1]

By RAY LYMAN WILBUR
AND
WILLIAM OPHÜLS

Following a meal of roast beef, string-bean salad with mayonnaise dressing, gelatin pudding, coffee and whipped cream, taken by a group of young people at a sorority supper held at Stanford University on November 25, 1913, twenty-four ate of the bean salad, and of these twelve were taken ill within the succeeding few days with symptoms of botulism. The string beans were from two separate lots: one dark green in color purchased at a grocery store and packed by a canning association, the others light green in color were put up the summer before at the home of one of the girls attending the dinner. These latter beans were apparently prepared by the process of sterilization recommended by the United States Department of Agriculture Bulletin, *i.e.*, boiling in the final container for one hour on three successive days. There was no food or meal taken in common by all of those poisoned except the one in question. Among those made ill was one of the waiters who had likewise partaken of the beans. The fact that two or three of the first patients had also eaten mushrooms confused the diagnosis slightly at first. Of the twelve taken ill one died about two weeks after the meal. All of the rest had bulbar disturbances of varying degree but all made a satisfactory recovery.

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The early symptoms came for the most part at the end of thirty-six to forty-eight hours, and because of the eye manifestations several first consulted an eye specialist, Dr. Howard Black, of Palo Alto, and he together with Dr. Thomas M. Williams were in attendance upon the patients whom I had the opportunity of studying. While there was marked variability in the course and seriousness of the disease picture, all were enough alike so that the description of one patient will illustrate the phenomena observed.

Typical Case. Female, aged twenty-three years, Tuesday evening, November 23, 1913, ate the dinner, including the canned string beans of the light green color together with a little rare roast beef. The following day she felt perfectly normal except that at ten in the evening the eyes felt strained after some sewing. Thursday morning, thirty-six hours after the meal, when the patient awoke, the eyes were out of focus, appetite was

FIG. 1.—Photomicrograph showing thrombus in vertebral artery.

not good, and she felt very tired. At night she had still no appetite, was nauseated, and vomited the noon meal apparently undigested. Friday morning, two and a half days after the meal, the eyes were worse, objects being seen double upon quick movement, and it was noticed that they had a tendency to be crossed. A peculiar mistiness of vision was also complained of. She was in bed until late in the afternoon, when she visited Dr. Black.

She had had some disturbance in swallowing previous to this time, and stated that it felt as if "something came up from below" that interfered with deglutition. The fourth day she remained in bed, was very constipated, and noticed a marked decrease in the amount of urine voided. There was pain at no time, except for occasional mild abdominal cramps, no headache, subnormal temperature, and a normal pulse. The fourth and fifth days the breathing became difficult at times, and swallowing was almost impossible. She complained of a dry throat with aggravating thirst. The sixth day there were periods of sense of suffocation, with a vague feeling of unrest and as if there might be difficulty in getting the next breath. The upper lids had begun to droop. The voice was nasal. Upon attempting to swallow liquids they passed back through the nose. The patient felt markedly weak.

Physical examination at this time showed ptosis of both upper eyelids, dilatation of the right pupil, sluggish reaction to light of both pupils, apparent paralysis of the internal rectus of the left eye, normal retina, inability to raise the head, control apparently having been lost of the muscles of the neck, inability to swallow, and absence of taste. The tongue was heavily coated and the throat was covered with a viscid, whitish mucus clinging to the mucous membrane. The soft palate could be raised, but was sluggish, particularly on the right side. The exudate upon the right tonsil was so marked that it resembled somewhat a diphtheritic membrane. The seventh day there was some change in the condition; occasional periods occurred when swallowing was more effective, and there was less tendency to strangle. On the eleventh day there was some improvement of the eyes, still less strangling on swallowing; the sensation of taste was keener, and the general condition improved. On the twelfth day the patient was able to move her head, but was unable to lift it except when she took hold of the braids of her hair and pulled the head forward. The eyes could be opened slightly, speech was less nasal and more distinct, and improvement in swallowing was marked. At the end of two weeks the patient was able to take soft diet freely, and at four weeks she was up in a chair for a couple of hours, complaining only of general weakness and inability to use her eyes. At the end of five weeks she was able to leave the hospital and return to her home and later to resume her regular work.

The above description is typical of the cases seen, and corresponds to the picture of botulism which was first clearly differentiated as a clinical entity by Van Ermengen, who, following his study of the epidemic of Ellezelles, demonstrated that the symptoms were due to a toxin formed by an anaërobic organism, the *Bacillus botulinus*. In the patients seen by me there was a wide variation in the severity of the disease, some having only transient disturb-

ance of vision or of swallowing, others such complaints as "jaws seemed very tired," "apparent inability to chew the food," "tongue seemed hard to move," "sleepy all the time," "could not walk fast," "throat filled up with mucus all the time," "tried to attend classes, legs and arms were almost powerless," "hard work climbing stairs," and "throat felt as if there was a shelf in it beyond which food could not pass but it did not hurt." The complaints of seeing double and of the mist passing over the eyes were comparatively common. The gradual onset of the symptoms and their marked variability were the most striking features. At one time a patient would show marked inability to swallow, while a little later a soft meal would be taken without difficulty. There was very little difference for some time in the severity of the clinical picture between the fatal case and some of the others. The details of these cases were reported by Dr. Thomas M. Williams at the meeting of the California State Medical Society in April, 1914.

Fatal Case. Young, healthy woman, aged twenty-three years. On the second morning following the ingestion of the meal at which the beans were taken she complained that objects were often seen double. There was no headache or vomiting, and urination was apparently as usual. A laxative had been taken because of constipation, and the bowels had acted. On the fourth morning the patient was unable to eat because of the inability to swallow. There was no pain. Later on in the day she swallowed with difficulty. On the sixth morning her mouth was dry, there was considerable thirst, no abdominal colic, no appetite, marked asthenia, with the muscular power in the left arm less than normal. The voice was slightly nasal, with inability to articulate distinctly. The temperature was 97.8° to 99°, and pulse 104. There was ptosis of both upper lids, both pupils were dilated, but reacted to light, with normal fundi. The breath was foul, the tongue coated and it and the pharynx covered with sticky, whitish, viscid mucus. There was considerable edema of the uvula. The condition did not change very much in the next few days except that the patient felt very weak, was unable to raise the head without help, at times would swallow well, at other times was unable to take the simplest food and the pulse became more rapid and dicrotic. The blood-pressure was normal. At one time she became quite talkative and complained that her jaws did not open naturally and she could not see well but for the most part she was quiet and slightly depressed. On the *tenth* day she brought up with very much difficulty some mucus which had been interfering greatly with her throat and had a period in the afternoon when she was unable to swallow,

had difficulty in breathing and cold extremities. Later on she was able to take an egg-nog but complained of a spontaneous choking sensation. In the night to the distress from these attacks was added an inability to breathe through the nose. On the *twelfth* day involuntary movements of the bowels occurred. Some relief from the choking, breathless sensation was gained by swabbing the throat. The patient vomited some dark green fluid after a large, soft involuntary stool and began to feel very warm and excited, axillary temperature going up to 100.4°. After a period of chills, great restlessness, choking sensation, increasing temperature, and higher pulse rate together with the signs of hypostatic pneumonia, the patient had

FIG. 2.—Photomicrograph showing thrombosis in small vein in brain tissue near oculomotor nucleus.

a collapse from which she recovered upon the intravenous administration, by Dr. Williams, of a normal salt solution. She vomited later a considerable amount of blood and although her breathing became more superficial and her weakness more evident, the sensorium remained perfectly intact.

On the *thirteenth* day she died following a respiratory disturbance apparently due to sudden paralysis of the diaphragm, since the heart continued to beat for some time. Various forms of stimulant and other treatment were administered without avail. The autopsy performed by Dr. William Ophüls was practically negative except for areas of collapse and bronchopneumonia in the posterior parts of the lungs, and certain lesions of the central nervous system, which will be described later.

Symptoms and Signs. When one sees a series of cases presenting such striking features as those enumerated in the two described above the difficulty of making a diagnosis of botulism is not great but it is easy to see how a sporadic case could be readily overlooked or confused with various other conditions such as luetic bulbar paralysis, anterior poliomyelitis, etc. The symptoms noted by the various writers who have described epidemics of this type are all of the same general character.

Digestive and Secretory Symptoms. Contrary to the usual idea of food poisoning there is apt to be freedom from pain except perhaps for some colic, with occasional vomiting, and only at times diarrhea, in patients who have been poisoned with botulismus toxin. Obstinate constipation is the rule, the intestinal tract being paralyzed by the ingested poison. Bürger[1] reports the washing out of food particles from the stomach eaten five days previously upon the evening of the day when the infected ham was taken for breakfast. Slow absorption resulting from this alimentary tract paralysis probably explains in part the gradual onset of the symptoms and also the finding by Kob of toxin in the blood of a child eight days after its ingestion. Very few signs of peristalsis were heard over patients seen by me except after the use of brisk cathartics and enemas. The late involuntary stools and the other gastro-intestinal features in some cases may be due to a central effect upon the vagus. The first stool passed in a patient was described by Van Ermengen[2] as dark and full of mucus. Anorexia is common and the foul breath, coated tongue, viscid, sticky, whitish mucous secretion with the generally dry mouth is accompanied apparently by a paralysis of the secretory activity of many glands (parotid enlarged at times) extending in some patients even to the lachrymal glands so that Schumacher[3] reports the inability of a woman to shed tears when told of her husband's death. At times tears are secreted freely and as in one of our patients the eyes appear watery and injected.

Nervous System. The most striking effect on the nervous system is the difficulty in vision with the normal background, dilated pupils,

[1] Med. Klinik, 1913, ix, 1846.
[2] Ztsch. f. Hygiene u. Infektionskrankheiten, 1897, xxvi, 1.
[3] Münch. Med. Woch., 1913, lx, 124.

ptosis, and paralysis of the various eye muscles with double vision and the disturbances in deglutition. Dizziness, sleeplessness, marked muscular weakness with no disturbance of the sensorium, no headache and no anesthesia or paresthesia are most characteristic. At times various paralyses of the different skeletal muscles, particularly about the neck, are seen. Practically all of the cranial nerves, except the I and II C.N., have shown involvement in described cases, *i. e.*, ptosis, mydriasis, disturbances of accommodation (III, IV, and VI C. N.), inability to cry (lachrymal nerve of V C. N.), dryness in the mouth (VII and IX C. N.), disturbance of deglutition partially due to lessened secretion and partially due to nervous disturbances leading to difficulty in chewing and the muscular side of swallowing (IX, X, and XI C. N.), mask-like expressions (VII C. N.), at times difficulty in hearing (VIII C. N.), variation in speech to aphonia (XII C. N.), obstipation and respiratory and cardiac disturbances (X C. N.). The retention of the urine and the occasional paralyses of muscles of the limbs indicate that the spinal cord may be damaged at times. The deep reflexes are not disturbed. Romberg's and Babinski's signs are both absent. No tremor and no spastic conditions have been described. We noted no angioneuroses of the skin. The sensation of the mucous membrane of the throat and mouth is dulled at times probably because of its dry condition.

Circulatory and Respiratory Disturbances. The temperature, pulse and respiration remain practically normal unless the vagus centre is involved or a secondary infection takes place. The blood-pressure was found normal in our patients, and no abnormalities were noted in the blood itself. The feeling of compression and oppression in the chest complained of by some patients is probably nervous and not circulatory in origin.

Genito-urinary System. A lessening in the amount of practically normal urine is usually seen. At times this is due to retention. There may be paralysis of the bladder detrusors or sphincters. The small amount of urine later is perhaps due to the inability to swallow. Twenty-four hours or longer passes in some patients before urine is voided.

Throughout it must be constantly remembered that the symptoms may be extremely acute and be followed by early death or they may

be gradually unfolded in their entirety, or that only one or two characteristic evidences may appear. The variations in the course of the disease may be due to the amount of toxin in the food eaten, to individual resistance or to the amount of vascular thrombosis present. The prognosis for eventual complete recovery is good if the early part of the illness is survived. In the cases here reported only one of the twelve patients succumbed, although no early difference in the severity of the clinical picture could be seen between this patient and some of the others who recovered. Death usually occurs during the first or second week, seldom later. Thirty to fifty per cent. is a common death rate. In the Ellezelles epidemic described by Van Ermengen only three of the thirty cases died.

Differential Diagnosis. The isolated case is the one that is most apt to lead to confusion in diagnosis, particularly with syphilis and poliomyelitis. When botulismus is severe enough to promptly endanger life the disease picture is usually so distinct as to permit of ready recognition. The prominence of the paralysis of the eye muscles often brings the patient first to the ophthalmologist, who must bear in mind that conditions varying from a nystagmus to an absolute immovability of the eyeballs, always with a normal retina, may occur in botulismus. Poliomyelitis, the so-called asthenic bulbar paralysis, cerebral syphilis, the various toxic ophthalmoplegias, rabies, diphtheria, poisoning with plant alkaloids (atropin, gelsemium, hyoscyamin, etc.), methyl alcohol, and ptomaines (methyl guanidin, ethyl endiamin, etc.) must all be ruled out before making a final diagnosis.

Anatomical Lesions (*W. Ophüls*). As a result of Van Ermengen's classical work the question of the pathology of botulismus appears to be well settled. The bacteriological findings have been confirmed by several later investigators, and his animal experiments hardly leave any doubt as to the etiology of the disease. Although the symptoms produced in the experimental animals by means of administration of the toxin of the Bacillus botulinus are perhaps not absolutely identical with those observed in human beings, they are similar enough to recall the symptom-complex of the disease in man and moreover they coincide entirely with the result of intoxication of similar animals treated directly with the spoiled foodstuffs.

Largely on the basis of the *clinical symptoms* one has assumed a specific action of the botulismus toxin upon the ganglion cells of the central nervous system although other effects of the poison have been observed, namely a marked paralyzing effect upon the gastro-intestinal canal and a tendency to the occurrence of multiple minute hemorrhages, more especially in the pons and medulla. The former, the paralysis of stomach and bowel, might also be ascribed to an affection of the motor ganglia of these organs, either centrally or peripherally.

This conception of a specific action of the toxin on the ganglion cells has been much strengthened by the histological findings in the central nervous system of animals subjected to the experimental intoxication. Van Ermengen in his original article[1] describes peculiar degenerative lesions in the ganglion cells of such animals which involve largely the Nissl granules, although the nucleus also appears sometimes affected. Of these changes he says, "There are almost none in the cerebrum or in the cranial nerves, but they are very pronounced in the spinal cord, less so in the medulla, in the pons and in the peduncles." He adds however "On the whole these lesions are very variable in intensity." He also finds small perivascular hemorrhages. Marinesco,[2] who studied the same material gives practically the same account of the alterations. He even speaks of a phagocytosis of the injured cells by neuroglical phagocytes. Kempner and Pollack[3] confirm these observations of Marinesco and of Van Ermengen, but believe that in their specimens, also obtained from animals treated with the botulismus toxin, they observed a still earlier lesion of the Nissl granules which they speak of as "Klumpige Schwellung." They did not find any evidence of phagocytosis. The question was reëxamined experimentally by Ossipoff[4] in 1900. He experimented upon monkeys, cats, and pigs as the animals most susceptible, and found lesions in the nerve cells similar to those described by Marinesco and others. He also believes to have found evidences of phagocytosis of the damagesd cell. He makes the following interesting statement "Within the hyper-

[1] Van Ermengen, Contribution a l'etude des intoxications alimentaires. Arch. de Pharmacodyn, 1897, iii, 213, 299.
[2] La Presse Méd., 1897, v, 43. [3] Deutsch. med. Woch., 1897, xxiii, 505.
[4] Ann. de l'Institut Pasteur, 1900, xiv, 769.

emic bloodvessels as well as on the outside of them there were found many white-blood corpuscles. In the vessels these corpuscles were sometimes bunched in masses." The importance of this statement will become more evident in the discussion of our own findings. On the basis of these findings Romer and Stein[1] attempted to localize more exactly the paresis of accommodation observed in some of the animals experimented upon and came to the conclusion that the disturbance is localized in the nucleus of the oculomotor nerve, on account of the degenerative lesions found in certain parts of the nucleus.

It is surprising how few human brains have been the object of a careful histologic investigation in this disease. Van Ermengen was unable to obtain any satisfactory material in his cases. Fischer,[2] who describes an outbreak of the disease due to spoiled beans, came to the conclusion, clinically, that the intoxication produced "central paralysis with successive elimination of certain motor nuclei in the brain stem of the vital centres in the floor of the fourth ventricle," also that it eventually caused a descending paralysis of the motor neurons in the anterior gray columns of the spinal cord. Parts of the brains of several of his cases were sent to the Pathological Institute at Giessen for examination, but apparently no characteristic lesions were found. In the latest publication by Bürger several new postmortem examinations on cases dead of botulism are mentioned, but in *one* of the records only there is this short allusion to specific lesions in the central nervous system: "In the cerebrum the ganglion cells are well preserved, but in the region of the oculomotorius they show commonly dust-like disintegration of the Nissl granules and excentric position of the nuclei." It is well to bear in mind in this connection how equivocal these finer lesions in the bodies of the ganglion cells still are. So far as I can see they are given less significance at the present time by neurologists, than they were shortly after their discovery by Nissl.

The brain in our case was obtained within twenty-four hours in a very good state of preservation. It has been remarked by others, that in botulism the tissues remain intact for an unusually long

[1] Graefe's Arch. f. Ophth., 1904, lviii, 291.
[2] Ztsch. f. klin. Med., 1906, lix, 58.

period of time which might suggest some interference with the normal autolytic ferments.

The gross findings at autopsy were entirely negative except for a moderate hyperemia of the cerebral vessels which was especially pronounced at the base of the brain and in the region of the fourth ventricle, where there also was found some edema. No hemorrhages could be made out with the naked eye on several sections through the brain stem. The internal organs were markedly hyperemic which was especially noticeable in liver, kidneys and intestines. This general hyperemia has been a constant finding in all cases of human botulism and is also found in the experimental disease in animals. The dilatation of all bloodvessels was also very evident in sections from all organs examined. Typical bronchopneumonic lesions were found in the lungs, which condition probably accelerated the death of the patient.

The following is a short description of the microscopic findings in the brain: The brain stem was sectioned transversely at different levels at the time of the autopsy and carefully hardened in frequently changed absolute alcohol. Numerous sections were made from all levels and special attention paid to the regions of the more important nuclei. Sections were obtained from all motor and some of the sensory nuclei on both sides. The nuclei studied were those of the oculomotorius (III), trochlearis (IV), trigeminus (V), abducens (VI), facialis (VII), acusticus (VIII), glossopharyngeus (IX), vagus (X), and hypoglossus (XII) nerves. The following lesions were found:

Thrombosis of the right arteria vertebralis at the lower end of the medulla and extending some distance into the arteria basilaris. The middle part of the arteria basilaris is free. The anterior portion of it is filled with thrombus. There are thrombi in a few of the pial branches of the basilar artery. Many pial veins at the base of the medulla and pons are filled with thrombi more especially on the right side and there are several thrombi in the veins of the tela chorioidea above the corpora quadrigemina and the posterior part of the third ventricle. All bloodvessels in the brain tissue are much distended and full of blood. Both in the ventral and in the dorsal parts of the brain stem one finds quite a few small throm-

bosed bloodvessels some of which are situated near important nuclei; for instance, one such was found near the right vagus nucleus, several in the nuclei of the olives, several in the substantia ferruginea, several in the right nucleus trochlearis, several near the right nucleus of the oculomotorius and similarly several near the left nucleus oculomotorius but somewhat further away from it. Small perivascular hemorrhages were encountered quite commonly about thrombosed veins and others. The thrombi in all places were very rich in polymorphonuclear leukocytes, but no bacteria could be demonstrated in spite of the use of various staining methods, including Weigert's modification of Gram's method. All thrombi were very rich in fibrin and contained comparatively few masses of conglutinated blood-platelets.

The Nissl granules stain unusually well in all sections, especially in the large motor ganglion cells. They are quite normal in size and arrangement. Nothing unusual could be detected in spite of specially careful study of them. The nuclei of the ganglion cells are perfectly normal.

Sections were also taken from various parts of the cortex of the cerebellum. There was no difference in the appearance of the cells from these other regions. Few thrombi were seen in the pial veins. The bloodvessels in the cortex are dilated and full of blood, but none show thrombosis or perivascular hemorrhages.

No thrombi were found in any other organs in spite of the study of many sections, except one in a vein in the submucosa of the intestine and the very beginning of the thrombotic process in a few of the dilated vessels in the ovarian cortex.

Anaërobic cultures were made from the intestinal contents both of the small and large intestines, from the cerebrospinal fluid, from the heart blood, and from the spleen. The cerebrospinal fluid and the heart blood was sterile and the Bacillus botulinus was not found in any of the other cultures.

I believe on the basis of these findings it will be necessary to change considerably our ideas in regard to the action of the botulinus toxin. No evidence was found to substantiate the hypothesis of a specific action of the toxin upon the nerve cells. The negative findings in regard to any disturbance in the Nissl granules in our

case are quite convincing in this regard in spite of the evidence to the contrary brought forward by other writers. The statement of Bürger[1] is so short and the lesions described in it are so slight, that it hardly deserves much serious attention. But even so, the fact remains that in our case the size and arrangement of the Nissl granules was quite perfect and if there should have been minor lesions they certainly were not sufficient to account for the severe clinical symptoms. So far as the positive findings in the experimental animals is concerned, it may be pointed out that in them the localization of the lesions as described by Marinesco and Van Ermengen and others does not coincide altogether with the clinical symptoms. They both emphasize the fact that the most marked involvement is found in the ganglion cells, both motor and sensory of the cord, whereas, in man at least, cord symptoms are late and rare and sensory symptoms have never been observed. The lack of histologic findings in the ganglion cells does not of course prove that the poison may not have a specific action upon the ganglion cells after all, but the matter remains a mere hypothesis which is greatly weakened by the positive finding of lesions which explain the clinical symptoms as well, if not more adequately.

There is present all evidence of a serious interference with the circulation in the meninges and in the brain which is most marked at the base of the brain, throughout the brain stem where numerous hemorrhages testify to the seriousness of circulatory disturbance. Associated with this disturbance of the circulation one finds multiple thromboses in the bloodvessels, both in the arteries and veins. The upper part of the right vertebral artery, the posterior part of the basilar artery and again the anterior part of the same vessel are completely obstructed by thrombi. Several of the branches of these arteries in the pia are filled with thrombi. There are thrombi in many veins in the pia and in the substance of the brain, several within or in the immediate vicinity of important nuclei.

The disturbance in the bloodvessels evidently consists in an extreme vasodilatation with great slowing of the blood-current and as such it is only part and parcel of a general paralysis of the vascular mechanism which has been observed and noted by all careful

[1] Loc. cit.

observers of cases of botulism. This has been usually referred to insufficient heart action. When we take into account, however, that the poison has a powerful paralyzing effect upon the involuntary muscles of the gastro-intestinal tract, as is shown by the prompt paralysis of the stomach and the obstinate constipation, it would appear probably that the poison might have a similar effect upon the muscular wall of the bloodvessels, either directly or indirectly through the vasomotor nerves, which would certainly have a tendency to at least contribute greatly to any interference with the circulation which might be partly due to poor heart action.

Why the circulation in all cases should be especially poor at the base of the brain, more especially in the pons and medulla, is not so evident. One might suggest, however, that the main blood-supply to these parts through the vertebral arteries is not so abundant as the blood-supply to the cerebrum from the internal carotid arteries.

The origin of the thromboses is also somewhat puzzling. I believe the existence of them in both arteries and veins excludes the idea of embolism.

It is also somewhat difficult to explain why we should have in these cases a tendency to thrombosis so exclusively in the bloodvessels of the brain, because in other organs very little evidence of thrombosis could be detected, but even if we assumed a pretty general tendency to thrombosis those in the bloodvessels in the brain stem would provoke the most prominent symptoms on account of the crowding of so many important centres at that point.

At all events in our case the evidences of severe disturbance of circulation associated with hemorrhages and thrombosis in the pons and medulla are clear and they are sufficient to explain the symptoms, whereas the assumption of specific action of the poison on certain ganglion cells, in our case, appears to be purely hypothetical.

Treatment. As soon as the possibility of botulism presents itself the most evident therapeutic procedure is to empty the stomach thoroughly with a stomach-tube, to wash out the large bowel and to leave in the stomach a brisk cathartic, castor oil or Epsom salts. Since the toxin is the cause of the symptoms and its absorption is slow because of the paralysis of the intestinal tract the above measures should be carried out even after several days. The patient

should be kept absolutely quiet, the body supplied with plenty of water, by rectum or under the skin if necessary, simple food given and great care used to prevent aspiration pneumonia. Strychnin seemed beneficial in the cases described in improving the action of the disturbed nerve centres. Other stimulants should be given as required. The vascular conditions above described indicate the possibility of complete recovery from a condition that seems hopeless and should lend encouragement to keeping up a hard fight against the disease, even to prolonged artificial respiration in case of respiratory failure. The specific serum treatment has been, so far as I know, not used in this country. Leuchs[1] and others have prepared a serum which is very effective in animals. Polyvalent sera have given the best results. In Berlin this serum is prepared by the Government. It is quite evident from the animal experiments that it would have to be near at hand and used promptly to be successful. That such sera should be kept in the various centres of the country is evident, as extensive botulism poisoning is apt to occur at any time.

Source of Poison. In attempting to determine the foodstuff responsible for the poisoning of the described patients each one was carefully questioned as to the foods partaken of at the meal in question. As noted there were two kinds of string beans, one dark in color from a grocery and put up by a prominent canners' association, and another light green in color, domestically prepared during the previous summer. These latter beans were tender and were served as salad with mayonnaise dressing without preliminary heating. They tasted well and were eaten freely by those to whom they were served. Some of the guests were given only the dark-colored beans and none of these were taken ill. The symptoms of poisoning were so delayed that none of the bean salad was obtainable for examination but two extra cans of the same lot of home-canned beans were placed at our disposal. The cans of tin were of quart size and the top was sealed with the hard red sealing wax often used for fruit jars. One of these contained perfectly normal-appearing beans in a small

[1] Ztsch. f. Hygiene, 1910, lxv, 55; Kolle und Wassermann, Bacillus Botulinus (Immunität), Handbuch der Pathogenen Mikroorganismen, 1912, iv, 939 (full bibliography given).

amount of juice, the other was "blown" somewhat and its contents fermented and slightly sour. Juice from both cans injected into animals had no evident toxic effects. In the fermented can Dr. R. H. Major found a long spore-bearing bacillus resembling somewhat the *Bacillus botulinus*. It was not that organism, but an unidentified one, apparently the so-called "*Bacillus Tourne*," well known and dreaded by fruit and catsup canners because of the resistance of its spores to heat and its ability to spoil a pack when mixed with the raw product. Evidently the spores of the above organism withstood the fractional sterilization of boiling of one hour on three successive days, so while we did not find the *Bacillus botulinus* in the beans we did find an organism which grows under similar conditions. The possibility then was present that had the beans been contaminated with *Bacillus botulinus* that organism could have developed in one of the cans. Therefore the question of whether the string beans may provide a suitable media is of the greatest interest in view of the present cases. The resistance of the spores of *Bacillus botulinus* to heat (while less than that of many anaërobes), the favorable anaërobic conditions, the optimum growth at ordinary temperatures, the ability to grow either in faintly alkaline or acid media, all favor the view that this is possible.

The famous Darmstadt epidemic was due to eating bean salad served uncooked. These were apparently ordinary beans (wax), (rather than string beans), prepared in a cooking school (Fischer).[1] Landmann[2] suggested the possibility that small contaminated meat particles were mixed with the beans but brought no evidence in support of this idea. The characteristic butyric acid (rancid) odor and slightly sour taste makes beans particularly dangerous when used for salad, since with the usual dressing a slightly sour taste is agreeable to most individuals. The destruction of the toxin by heat was well illustrated in Darmstadt by the man who came late to the celebration and thinking the beans were being served as a vegetable and not as a salad, heated them along with other food and suffered no consequences. That canned green beans may also serve as a media for the growth of other organisms is shown by

[1] Ztsch. f. klin. Med., 1906, lix.

[2] Hyg. Rundschau, 1904, xiv, 449.

the epidemic in Leipzig in 1906, described by Rolly,[1] where the *Bacillus coli* and *Bacillus paratyphoid B* were later isolated from them. In California several instances of poisoning resembling botulismus have come to our attention. Sheppard[2] described in a graphic manner the typical and fatal poisoning of two men and a woman following the eating of canned pork and beans while on a camping trip. Peck[3] reported a similar and more extensive poisoning with eleven deaths at Sawtelle, Cal., in which he thought that canned pears were responsible.

In order to study the canned goods upon which the *Bacillus botulinus* would grow, with the assistance of Drs. E. C. Dickson and E. G. Cary, a series of experiments were begun with a culture of *Bacillus botulinus* obtained from the New York Museum of Natural History by inoculating a number of cans of beans and keeping them under various conditions at various temperatures. Up to the present one of the cans tested had a slightly pungent smell and rabbits inoculated with the juice died with symptoms suggestive of botulism. The experiments will not be complete for some months but they apparently point to string beans in sealed cans as a media upon which the *Bacillus botulinus* will grow. Further we cannot go at present. Van Ermengen[4] has carefully worked out the details of the growth of this organism, its toxin and its destruction under varying conditions and they need not be reviewed here. The only record found of this organism occurring in nature was that of Kempner and Pollack who found it in pigs' feces. We have as yet been unable to find out whether pigs were kept near the beans in question or whether they were fertilized with pigs' feces. It is fortunate that an organism with such possibilities for harm is rare.

Nevertheless the greatest care should be used in the preparation of all canned foodstuffs, particularly those kept under anaërobic conditions and apt to be eaten uncooked, to see that sufficient steam pressure and heat is used to kill all organisms and their spores. The sterilization under high pressure in vogue with all large canning

[1] Münch. med. Woch., 1906, liii, 1798.
[2] South. California Pract., 1907, xxii, 370.
[3] Ibid., 1910, xxv, 121.
[4] Handbuch der Pathogenen Mikroorganismen (Kolle und Wassermann), 1912, iv, 909 (with full bibliography).

companies makes their pack safe, but with the variability in domestic preparation the least rancid odor should lead to rejection of canned food and all vegetables should be reheated before being served. A long series of experiments on the penetration of heat into the interior of cans in preserving meats, etc., have been made by Bischoff u. Wintgen,[1] Pfuhl,[2] Woeffhügel and Hueppe[3] and others, and the need of steam pressure as well as heat is emphasized. Bolduan[4] describes the work of Belser and others on "blown cans" and found that a number of different bacteria more or less resistant to heat were present.

The possible relationship of epidemics to Kalfieber (milk sickness) because of its similarity to botulism must be borne in mind (Crawford,[5] Schneidemühl).[6]

Conclusions. 1. The twelve cases reported presented the typical clinical picture of botulism apparently due to the eating of domestically prepared canned string beans, served without preliminary heating. That string beans may act as a culture media for the *Bacillus botulinus* is possible, and is being further investigated. The methods of sterilization under pressure in use by canning factories seems to preclude the possibility of the growth of *Bacillus botulinus* in their pack.

2. Vascular thromboses were found about the brain stem in a patient dying with the symptoms of botulism. Such lesions explain better the clinical phenomena observed than does the more or less hypothetical assumption of a specific action of the botulin on certain ganglion cells.

[1] Ztsch. f. Hyg., 1900, xxxiv, 496.
[2] Ibid., 1904, xlviii, 121.
[3] Mitt. a. dem kaiserlichen Gesundheite Amte., i, 395.
[4] Food Poisoning, Treat & Co., 1909, p. 104.
[5] United States Department of Agriculture, Bureau of Plant Industry Bulletin, 1908, No. 121, p. 5.
[6] Centralbl. f. Bakteriol., 1898, xxiv, 577 to 619.

STUDIES IN EXPERIMENTAL ATHEROSCLEROSIS

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A Preliminary Report. In the present communication the protocols of the experiments will not be reproduced in detail nor will extensive literature that has gathered about the problems of atherosclerosis be discussed; and lastly, definite conclusions as to the result of the experiments will not be warranted. It is reserved for a future communication, when experiments still under way will have been concluded, and more definite knowledge as to the histological and chemical results may have been obtained, to report more in detail and with a critical appreciation of the literature.

All the investigations here reported have been done on dogs. The spontaneous occurrence of atherosclerosis in dogs, its histological structure, and the question of its greater or less analogy to human atherosclerosis are problems that have not received the attention that they deserve. In the text-books on animal pathology little is to be found on the subject, and until recently the general opinion appears to have been that dogs were not disposed to atherosclerosis, and that if it occurred at all it was exceptional. Latterly it has been discovered that dogs are indeed subject to spontaneous atherosclerosis. The process is said to be limited, however, to the large vessels. The early stages appear as round or more oval or lengthwise patches of a whitish or pale yellowish and pinkish color, and are somewhat elevated above the surface of the intima. These sclerotic areas, it is said, are met with principally in localizations where the blood is apt to impinge with greater force against the wall of the vessel, for example, places where the vessel takes a sudden turn in a new direction, or where other vessels branch off from the

main trunk. The later stage of the atherosclerotic process is described in text-books as showing atrophy of intima and media, extensive fatty degeneration, and calcification.[1] Della Vida[2] has seen spontaneous atherosclerosis in a large percentage of old dogs.[3]

Notwithstanding, however, that up to the present our knowledge of atherosclerotic processes in dogs is scant and insufficient, there seems to be no reasonable doubt that a process in many respects analogous to human atherosclerosis does occur. Granting this, for many years the writer has believed, and quite independently of experiments on dogs published in recent years, that if the possibility existed of producing experimentally a process that resembled in any way human atherosclerosis, one should be able to produce it in dogs, and not alone in rabbits. As the dog is omnivorous, it might be assumed, although it does not necessarily follow, that the metabolic conditions would approach more nearly those of human beings than is the case in the herbivorous rabbit. It is also an advantage that the disturbing median necrosis and calcification to which the aorta of the rabbit is readily disposed is negligible in experiments on dogs. It is as yet not possible to state with certainty whether the structure of the aorta of dogs resembles the human aorta more closely than does that of the rabbit.

Much has been said and written concerning high blood-pressure; various intoxications, such as lead and nicotin, and also infections with bacteria and bacterial products are regarded as important factors in the etiology of atherosclerosis. It was proposed to investigate some of these questions experimentally.

The first series of experiments was done during the greater part of 1908 and the first half of 1909. The writer wishes to express his thanks to Dr. William H. Park through whose courtesy and interest it was possible to carry on this work in the laboratories of the New York Board of Health.

In this entire series the material to be tested was applied parenterally. The injections were supposed to be made into the jugular

[1] Hytyra and Marek, Spec. Path, und Therap. der Hausthiere, 1910, vol. x, p. 1100. Lyding Zeitschrift f. Thiermedizin, 1907, vol. xi, p. 359.

[2] Deutsch. med. Woch., 1913, No. 45, p. 2200.

[3] Celli, Manuale dell' Igienista, 1912, IV Ed., vol. ii, Part 2, p. 1148.

vein, with all proper regard to asepsis. It is not always easy to get the needle into the jugular, and it probably happened very often that the injection became subcutaneous instead of intravenous.

Lead. Former experience with rabbits has shown that the ordinary soluble lead salts were unsuited for hypodermic application that was to extend over any considerable length of time. The local reactions in every case were such as very soon to render the injections impossible. It was found, however, that the triethylacetate of lead, as employed by Harnack[1] in his experiments, served our purpose admirably. Dr. Robert Emerson, then of Boston, prepared the salt in perfect purity. There was little or no local reaction, and the injections could thus be carried on *ad libitum*.

It should be mentioned that the blood-pressure of our dogs was not tested, but that Harnack, contrary to the generally accepted opinion, found that in his animals the lead injections caused the blood-pressure to rise. Two dogs were tested.

Dog I. The injections were commenced on April 3, 1908. The animal was found dead in his cage on May 26, 1908. The symptoms corresponded closely to those described by Harnack. The temperature ranged from 101° to 104$\frac{3}{5}$° F. There was considerable excitement, diarrhea, toward the end of the experiment bloody stools, and paralysis of the hind legs. During the fifty-five days of the experiment the dog received injections amounting to 290 minims of a 1 per cent. solution.

Dog II. From June 1, 1908 to August 18, 1908, when the dog was found dead. The symptoms were the same as in the first dog. The total amount injected was 590 minims. In both dogs no lesion could be found in the aorta or any other large vessel. Harnack also failed to find any lesion in the vascular system of his dogs.

Nicotin. Dog I. The experiment lasted from May 4 to December 6, 1908, a period of about 7 months. The dog was found dead in the cage. Fifteen minims of a 1 per cent. solution of nicotin were injected at varying intervals, according to the condition of the dog, usually every two or three days. There were never any convulsions. No lesions were present in the arteries.

[1] Ueber die Wirkung des Bleis auf den thierischen Organismus, Arch. f. Exp. Path. und Pharmak., 1878, ix, 152.

Diphtheria Toxin.[1] Dog I. From May 12 to July 18, 1908, about 67 days. Commencing with a single drop, the quantity injected was gradually increased until 1 c.c. was injected, after which the dog was found dead in the cage. No sclerotic lesions were present in any of the vessels.

Dog II. From April 4 to April 26, 1908. Death after 22 days. Temperature up to 104$\frac{1}{5}$° F. One drop of the toxin was injected; two drops twice only. The result as to the arteries was negative.

Dog III. From March 17 to April 9, 1909. The solution used was 1-150. One to ten drops were injected. Death in about three weeks. Temperature up to 104$\frac{1}{4}$° F. Negative result.

Experiments with Bacteria. The cultures were obtained from the Board of Health laboratories, and were of various strains. I am also indebted to Dr. Alfred F. Hess, who had the kindness to control the purity of the cultures. For the success of these experiments it was necessary to keep the animals alive as long as possible, but in a condition of mild sepsis. For this reason cultures of but moderate virulence were employed.

Staphylococcus Aureus. Dog I. Experiments commenced March 10, 1908, and the dog was killed on June 13, 1908, after about three months. The injections, commencing with a single loop, suspended in normal saline, were gradually increased to the injection of an entire agar slant. The temperatures ranged from 100° to 104$\frac{2}{5}$° F., showing the characteristic septic temperature curve. Result as to bloodvessels negative.

Dog II. October 30, 1908 to March 15, 1909. Animal found dead after about four and a half months. In this case the cultures were not so virulent as in the former experiment, and sepsis was therefore not so marked, though nearly always an entire slant was injected. Temperatures from 101° to 103$\frac{4}{5}$° F. No arterial lesion.

Saltykow reported some time ago that he had obtained positive results from the injection of staphylococcus in rabbits. In his most recent publication,[2] however, he is inclined to attribute the positive result not to the injections of staphylococcus, but to the milk with which the rabbits were fed.

[1] The diphtheria toxin was procured from the laboratories of the New York Board of Health.

[2] Saltykow, Experimentelle Atherosklerose, Ziegler's Beiträge, lvii, Hft. 3, 415.

Streptococcus Pyogenes Albus. Dog I. From October 30, 1908, to death, a little over five months, on April 9, 1909. Cultures were not very virulent. Whole agar slants were used. Temperature varied in the neighborhood of 103° F. Result as to arteries negative.

Colon Bacillus. Dog I. From March 10, 1908, to October 15, 1908. Animal killed after about seven months. Temperature ranged between $99\frac{3}{5}°$ and $103\frac{2}{5}°$ F. Animal gained weight during the experiment. Arteries normal.

Dog II. October 30, 1908; found dead after $5\frac{3}{4}$ months, on April 17, 1909. The animal had developed a number of abscesses. Temperature ranged from 102° to 104° F. Arteries normal.

Typhoid Bacillus. Dog I. October 30, 1908. Killed after about six months, on April 30, 1909. Temperature ranged from $101\frac{1}{2}°$ to $103\frac{1}{5}°$ F. Profuse diarrhea and frequent bloody stools. Arteries without lesion.

I was compelled to interrupt these studies for a number of years, but was enabled to take them up again in January, 1913.[1]

It has been shown in former experiments that the injection of adrenalin alone seemed to have no effect upon the dog's arteries.[2] It was now proposed to test the effect of the high blood-pressure caused by the adrenalin, combined with severe bodily exertion, with special reference to the purely mechanical "*Abnutzungstheorie*" that had at one time been generally and favorably received. For this purpose a treadmill was constructed, so that two dogs could run on it simultaneously and at the same speed, and could not stand still during the period of exercise; they were, moreover, so harnessed that they could not lie down. One dog was injected with gradually increasing doses of adrenalin 1 to 1000, usually every other day, sometimes several days in succession. It was intended to inject the adrenalin into the jugular vein, but the injections were probably mostly subcutaneous.[3]

[1] I wish to express here my grateful obligations to Professor F. S. Lee, Director of the Physiological Department of the College of Physicians and Surgeons, Columbia University, for placing the conveniences of his laboratory at my disposal.

[2] Otto, Ueber Arteriosklerose bei Thieren und ihr Verhältniss zur Menschlichen Arteriosklerose, Virch. Arch., 1911, cciii, 352. Otto finds that dogs are much less sensitive to adrenalin than rabbits, but claims some positive results in the dogs' aortas after the injection of astoundingly large quantities of adrenalin.

[3] I am indebted to Dr. B. S. Oppenheimer for carrying out the injections and for performing the autopsies on both dogs.

The second dog served as a control; it received no injection, but worked steadily together with the other dog in the treadmill. The experiment was started on January 20, 1913. Running in the treadmill began with twenty-five minutes in the morning and thirty minutes in the afternoon. Occasionally for a day or two there was no running, but on the whole the work went on fairly steadily, and was increased gradually so that at the end of the experiment when, on June 2, 1913, both dogs were killed, they ran at top speed for almost four hours in the morning and about three hours in the afternoon. The adrenalin injections began with ten minims, and the dose was gradually increased so that at the end of about four months the dog received eighty minims at a single injection, the total amount injected in sixty injections during 130 days being 1.676 grams. These doses are minute compared to the huge quantities injected by Otto, who injected 49.5 grams of pure adrenalin in the course of five months by means of seventy-eight injections. The initial weight of the adrenalin dog was 11,870 grams; he gradually gained in weight, so that on April 4 he reached his highest weight of 15,300 grams; from then on he gradually lost again, so that at death he had again come down to about his original weight. The control dog weighed 10,220 grams; on March 16 had gained about 2 kilos, and at death weighed about 8780 grams. A very careful study of the bloodvessels after death failed to show any arterial lesion in either dog.

It was soon noticed that, while the adrenalin dog was active and happy, and was practically untiring in running the treadmill, and always at top speed, the control dog was very soon tired, dispirited, and at the end of his forced run completely played out. It is worth noticing, also, that the adrenalin dog developed no glycosuria. These facts correspond with Cannon's recently expressed views.

The uniformly negative result of all these experiments with reference to the arteries was calculated to impress one very strongly with the conviction that mere mechanical conditions, as well as intoxications and bacterial infections of various kinds, were not, at least in the dog, determining factors, and that parenteral methods were not likely to lead to any results. In the meantime, moreover, the researches of Aschoff, Anitschkow, Chalatow, Ignatowsky,

Saltykow, Steinbiss, and others had been published, from which it appeared that lesions resembling human atherosclerosis very closely, could be produced principally in rabbits, by feeding these animals on proteins and lipoids, especially cholesterin. Following along these lines, and on the theory that atherosclerosis was probably caused by chemical rather than merely mechanical influences, another set of experiments was undertaken to test the possible effects of various kinds of chemical substances added to the food of the animals.

From the fact that chondroitin sulphuric acid can be obtained in comparatively large quantities from the arteries, and especially the aorta, it was thought that adding this substance to the ordinary food of dogs might possibly give some results.[1] The dog, a healthy male fox terrier, was fed in the usual way with bread and meat. From October 24, 1913, a capsule containing 0.5 gram of the soda salt of chondroitin sulphuric acid was added to his daily meal until November 25, 1913. No capsules were then given until December 6. After that 1 gram of the salt was given daily, until December 30. The dog became ill with an abscess below the right ear, from which he recovered, and fed well most of the time. The capsules did not seem to affect him. The animal died on January 18, 1914, nearly three months after the beginning of the experiment. His weight varied according to his general condition, decreasing when the animal was ill, increasing so that at one time he gained $1\frac{1}{4}$ kilos, and at his death weighing about the same as when the experiment started. The total quantity of chondroitin sulphuric acid salt consumed was 47 grams. The cholesterin content of the blood appeared to be a little below the normal, being 0.001, while the normal for dogs is about 0.00137.[2] The autopsy showed normal aorta and large vessels.

It was now proposed to feed dogs on bread and cotton-seed oil, either without any or with only a very small quantity of protein in the food. It was assumed at first that the animals could consume

[1] I am indebted to Dr. P. A. Levene, of The Rockefeller Institute for Medical Research, for placing a great quantity of the chemically pure soda salt of chondroitin sulphuric acid at my disposal.

[2] S. Edwin Henes, Jr. (Deutsch. Arch. f. klin. Med., 1913, cxi, 122), kindly made the cholesterin determinations for me.

about 200 c.c. of oil daily, but it was soon found that about 50 c.c were all that they could manage and keep in fair condition. The low protein diet was probably not necessary.

Dog. I. Experiment commenced November 8, 1913. The oil was rapidly increased to 200 c.c. per day. For the first few days the dog ate the food. After that he would eat only one-third of his daily meal, and at times he would not touch the food at all. He was killed in a fight with another dog on December 6, having lost about a kilo in weight.

The cholesterin content of the blood was not determined. The autopsy showed normal vessels.

Dog II. Experiment commenced December 11, 1913. The dog was given bread, 2 ounces of meat, and 150 c.c. of cotton-seed oil. The dog ate all the food for three days, after which he sometimes took one-third, one-half, or sometimes the whole. On January 10, 1914, the oil was reduced to 50 c.c. From then on the dog ate all that was given him, till death on January 21, 1914. His weight remained about the same till the end, when he lost about 1 kilo.

The cholesterin content was 0.00225, almost double the normal. The autopsy showed pneumonia and a duodenal ulcer. There were a number of slight fatty streaks in the aorta.

Dog III. Experiment commenced on November 29, 1913. The dog was given bread, 2 ounces of meat, and 150 c.c. of oil, which was reduced on January 6 to 50 c.c. From December 23 to January 28 meat was taken away altogether; the dog ate bread and oil only. It was attempted to make him run in the treadmill; for a number of days he could be made to work for an hour or even more. He developed an abscess on the jaw, so that he could run only at irregular intervals. Then convulsions set in, and the running had to be stopped altogether. He was killed on January 31, the experiment lasting about two months. The weight increased slightly at first, then decreased somewhat, but at death was about the same as at the beginning, notwithstanding attacks of vomiting and diarrhea, besides convulsions.

The cholesterin content of the blood was 0.00228, also markedly above the normal. The anatomical diagnosis and autopsy showed

adherent pericardium, dilatation of heart, fatty deposits in the liver and kidneys, pulmonary emphysema, intestinal parasites, and fine fatty striæ in the aorta.

Uranium Nitrate and Oil. The oil feeding was then combined with uranium nephritis. On November 19, 1913, a dog injected subcutaneously with 1 c.c. of a solution of uranium nitrate 0.5 to 100. The injection was repeated the next day. Typical symptoms of severe uranium nephritis followed. He was fed with oil, soon reduced to 50 c.c., bread, and two ounces of meat. On November 6 the meat was taken away entirely, and the dog ate well most of the time. On January 11, 1914, the meat was given again. The animal died on February 12, 1914, nearly three months after the beginning of the experiment. He received altogether 6 c.c. of uranium nitrate solution in five injections. The urine at death had specific gravity of 1018, albumin 0.3 per cent. (Esbach), some red cells, and numerous casts, mostly hyaline. He lost steadily in weight, altogether about 2580 grams.

The cholesterin content of the blood was low, being only 0.00013. The autopsy showed typical uranium nephritis and infarction of the lung. There were no changes in the aorta or large vessels.

A second uranium-oil dog died eighteen days after the beginning of the experiment, without showing any special lesions besides nephritis.

Cholesterin. On January 27, 1914, an experiment was commenced with feeding cholesterin.

Dog I. The dog received bread, meat, 50 c.c. of cotton-seed oil, and every other day a capsule of 0.5 gram of pure cholesterin (Merck). It was not proposed to give the large doses of cholesterin which other investigators have given to rabbits and dogs, the idea being not to go beyond normal conditions more than was absolutely necessary. The animal took his food well until about the middle of February; at that time the oil was stopped, and from February 25th on he took 0.5 gram of cholesterin daily with his bread and meat. Repeated attempts to make him run on the treadmill failed, on account of his feet becoming sore after running a day or two. After about two and one-half months from the beginning of the experiment the animal died on April 8, 1914. The original

weight of 6700 grams decreased steadily, so that at death he weighed only 2400 grams. The autopsy showed pneumonia in the lungs; there were numerous small but quite distinct fatty patches and striæ in the aorta. The total quantity of cholesterin consumed was 25 grams. The cholesterin content of the blood-serum was 0.001808.

Dog II. February 5, 1914. Bread, two ounces of meat, 50 c.c. of oil, and 0.5 gram cholesterin were given every other day. The oil was stopped after twelve days. From February 25th 0.5 gram of cholesterin was given daily. The dog ate well from the time the oil was stopped, and was found dead on March 19, 1914. His weight had decreased about 900 grams. During the one and one-half months he had consumed 16 grams of cholesterin. The cholesterin content of the blood-serum was 0.00196. The autopsy showed ascites, probably due to nephritis; there was a small, cartilaginous patch in the sinus above the posterior aortic cusp, surrounded by a yellowish area of hypertrophied intima; there were besides a number of hypertrophic spots in the thoracic aorta. The bile in the gall-bladder contained large quantities of doubly refracting cholesterin crystals.

Hydrochloric Acid. A casual remark of Dr. P. A. Levene suggested the simple procedure of adding dilute hydrochloric acid to the dog's food, and thus producing a chronic hyperacidity.

Dog I. Beginning October 24, 1913, at first 20, after a few days 40, then 50, and finally 60 drops of dilute muriatic acid were added to the dog's ordinary food of bread and meat. The animal took the acid without any difficulty, and fed well till the last few days before death, which occurred on December 13, 1913, about two months after the beginning of the experiment. Though the dog took all his food and seemed perfectly well, he nevertheless lost just 3 kilos. The cholesterin content of the blood was not made in this case. The autopsy showed faint yellowish streaks just above the sinuses, behind the pulmonary cusps. The aortic cusps were normal. In the abdominal aorta, about 4.5 cm. above bifurcation, several raised patches of pinkish-yellow color were seen, somewhat irregular in shape, and with the surface wrinkled, the long axis parallel to the long axis of the vessel; there were some patches

also around the orifices of efferent vessels. Transverse ridges are marked in some of these patches, especially in several that are situated in the internal iliacs. Some similar patches are also recognizable in the carotids. There was considerable edema of the left lung, but no pneumonia. The cause of death is uncertain.

Dog II. Beginning December 22, 1913, dilute muriatic acid was added to the food, so that after twenty-one days the daily quantity was sixty drops, which after that was not increased. The dog was killed on March 25, 1914, three months after the beginning of the experiment. The animal was well during the entire time, and ate greedily. He was not full-grown when the experiment was started, but grew steadily, and had gained three kilos when killed. The cholesterin content of the blood-serum was 0.00159, just a trifle above the normal. At autopsy the dog was found to be well nourished, with good adipose tissue. The heart contained numerous *Filaria mitis;* the endocardium of the left ventricle was somewhat milky. No valvular lesions were present. Immediately above the aortic cusps in the sinuses of Valsalva, also near the origin of the left carotid, and especially in the abdominal aorta, and there again, most pronounced in its lower part, there were grayish-yellow patches slightly raised above the surface of the intima. The largest patch was situated near the origin of the innominate artery, and around this the aorta is decidedly thin. The iliac arteries showed distinct transverse striation with yellowish-gray and slightly raised mottling. There was nothing abnormal in the carotid and renal arteries. Otherwise there were no gross lesions.

Discussion. In reviewing briefly the outcome of all the experiments thus far reported, one fact stands out prominently; namely, that all the injection experiments failed absolutely to yield any positive result. Neither the poisoning with nicotin or lead, nor the infections with bacteria or bacterial products, appeared to afford the slightest evidence of atherosclerotic lesions in the aorta, or in any other vessel or organ of the dogs treated. If reasoning by analogy be permitted, it may be assumed that if a bacterial infection in man, which rarely lasts longer than a few weeks, is supposed to be an important etiological factor in subsequent atherosclerosis; then bacterial infections in dogs, prolonged for many months, and

finally ending in death, might reasonably be expected to cause some atherosclerotic change.

In the case of the two dogs running in the treadmill, the objection might be raised that, though the strength of the animals was taxed to the utmost, the experiment did not last long enough to cause any damage. This objection, however, loses much of its weight when one finds from the last group of experiments that positive results can be brought about in time equally short or even shorter.

This last group of experiments has already, though still far from concluded, apparently furnished some points of interest. Chondroitin sulphuric acid does not seem to be effective, and does not require further discussion. All the other experiments, with the exception of two dogs to whom dilute hydrochloric acid was given, were undertaken for the purpose of studying the now generally conceded causal relation between cholesterin and the atherosclerotic process in man, as well as in the rabbit. Pure cholesterin (Merck) was given only in two cases. The other dogs took cotton-seed oil, not only because this was less expensive than cholesterin, but also because it was thought probable that this oil contained sufficient lipoid material to answer every purpose. It was not proposed to administer the colossal quantities of cholesterin which some investigators had employed, and which exceeded by far all that either man or rabbit would ever consume under natural conditions.

In all the oil and cholesterin dogs, with but one exception, atherosclerotic lesions were found. It is true, however, that only the very earliest stages appeared; *i. e.*, the fine yellowish striæ, and the fatty patches, in their gross appearance closely resembling the same structures so familiar in human aortas.

The one exception was the dog with uranium nephritis. On general principles one would have expected that an oil-fed dog with chronic uranium nephritis would be much more likely to develop atherosclerosis than a dog with sound kidneys. This seems not to have been the case. Neither in the aorta, the renal artery, nor in the kidneys—in fact, in none of the vessels or organs of the nephritic dog—could any trace of atherosclerosis be found. The cholesterin content of the blood-serum in this dog was much lower than in any other dog. It will be the subject for further study to arrive at an understanding regarding these phenomena.

In the aorta of the first acid-fed dog, as described above, there were found not only the fine, fatty striæ in the thoracic aorta, but quite large, raised, sclerotic patches in the lower portion of the abdominal aorta and in the external iliacs. These patches closely resembled those atherosclerotic areas in human beings that have not yet become ulcerated or calcified. This dog, however, was about four years old. The obvious objection was therefore that the atherosclerosis in his case might have been spontaneous and entirely independent of the acid feeding. A young and growing dog was therefore subjected to the same treatment, and for a somewhat longer time, with the result that atherosclerotic changes similar to those in the first dog were now manifest over a considerably greater area of the aorta, both thoracic and abdominal, but more pronounced in the abdominal aorta. Though only two dogs have thus far been fed with hydrochloric acid, the possibility cannot be denied, especially in view of the numerous negative results with other methods, that these positive results are not mere coincidences, but are probably due to the hydrochloric acid. Further investigations are necessary, and are under way.[1]

While writing this communication, the work of Oswald Loeb[2] has come to my notice. He describes results similar to mine in two dogs which he fed with large doses of lactic acid and kept on an exceedingly low protein diet. The detailed reports of his experiments, and especially the microscopic findings, have not yet been published. No diminished protein diet was given to our dogs. They fed well on their usual diet of bread and meat, thus showing the sclerotic affection of the large vessels was in all likelihood due to the acid, and that it was probably immaterial whether the dogs ate meat or not.

The histological structure of this canine atherosclerosis has not yet been completely studied in all its details, but it has been ascertained that the lesions are primarily and principally localized in the intima. The intima of the dog's aorta, however, appears to differ

[1] Since writing the above, I have examined a third dog. The animal, scarcely one year old, died of pneumonia after having had acid feeding only for three weeks. He too showed a number of typical yellowish patches in the arch of the aorta.

[2] Ueber experimentelle Arterien-veränderungen, etc. Deutsch. med. Woch., September, 1913, No. 38, 1819.

Fig. 1.—Section through a sclerotic patch from the aorta of an acid-fed dog. Weigert-Van Giesen stain shows the proliferation of endothelial cells and the typical hypertrophy of the intima.

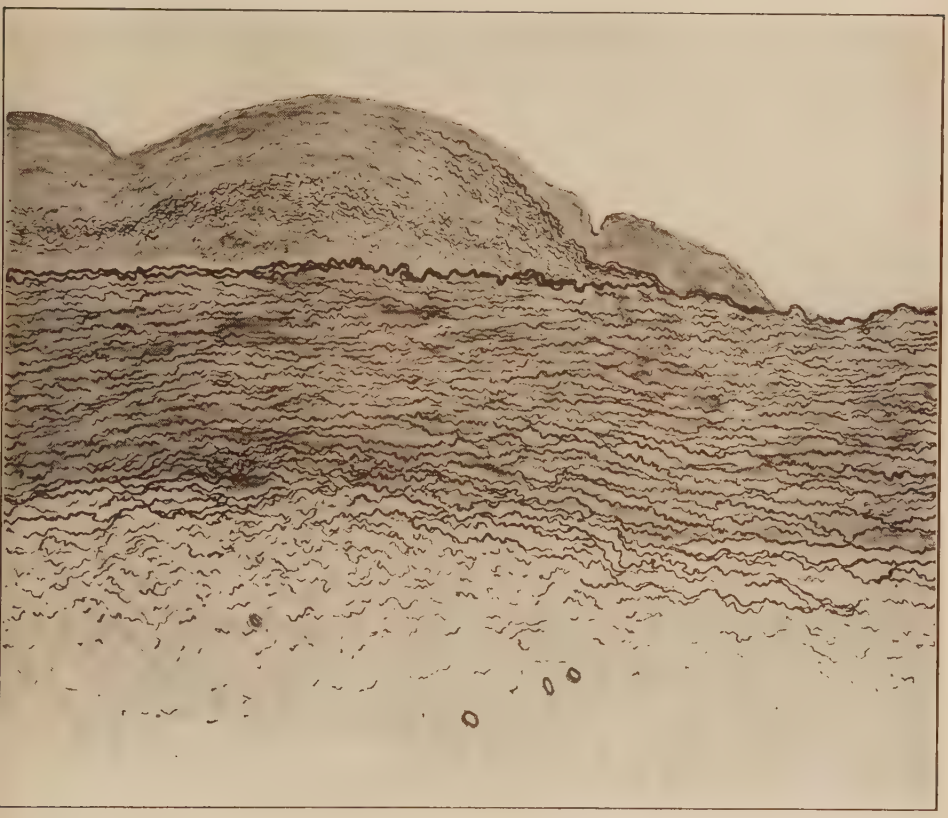


Fig. 2.—Section through the same aorta. Weigert elastic stain shows splitting off of elastic fibers from the elastica interna.

somewhat in its structure from that as found in man and in the rabbit. It would appear that under normal conditions the elastica interna is covered by a single layer, possibly by several fine layers, of endothelial cells. Fibrous or muscular tissue is nowhere perceptible. The very earliest beginning of the sclerotic process is marked by a proliferation of rather large, flat cells, in all probability of endothelial origin. Notwithstanding protracted search, and aided by the best technical methods and all sorts of stains, nothing in any way resembling the macrophages or the large amebic leukocytes described by Saltykow could be found (Fig. 1). Almost simultaneously with the appearance of these large cells, elastic fibers begin to be split off from the elastica interna, and the whole process, as described by Jores takes place (Fig. 2). A larger or smaller elevation or excrescence is thus formed, the base of which is still the elastica interna, and for some distance there can also be recognized one or two rows of those peculiar large endothelial-like cells, at the base of the elevation, and resting immediately upon the elastica. Between the newly split-off elastic fibers which form, as it were, the skeleton of the little excrescence, there now develops a more or less swollen and succulent connective tissue, and possibly also some muscular fibers. In the meanwhile, and in that portion of the media underlying the newly formed elevated patch, the elastic fibers are beginning to give way, and the tissues there are also in a swollen and succulent state. No aggregation of leukocytes, or anything else pointing to an inflammatory process, could be made out. In some text-books it is stated that calcification has been found in the spontaneous atherosclerosis of dogs, and it is perhaps not improbable that calcification would soon have followed the developments just described had the experiments lasted sufficiently long. Further investigation is required to clear up this point. It does not appear unreasonable to presume that the calcium metabolism in dogs, as well as in other omnivorous animals, differs from that of the rabbit, in which calcification, primarily in the media, occurs early and often spontaneously.

Simultaneously with the first appearance of the proliferating cells, and only among them and not in the normal intima, minute sudanophil droplets are seen contained in the upper portions of the pro-

liferating cells and also lying free above and between them. Very soon they are found in the media and down to the adventitia. As the process proceeds, the droplets become larger, sometimes run together, but never have we found them of the size and number as described in the rabbit and in man. They are most numerous in those fatty striæ and elevated fatty patches that we found in the aortas of the oil-fed, and especially of the cholesterin-fed dogs (Fig. 3), but they also occur with great constancy, though very much smaller in size, in the acid-fed dogs. They stain readily with Sudan III and Scharlach R; but they are optically inactive, and therefore are probably not cholesterin but some other as yet undetermined fatty or lipoid substance. It is a striking fact that, while the bile of the cholesterin-fed dogs contained innumerable doubly refracting cholesterin crystals, not a single one could be found in the arteries, the liver, and the adrenals. Chalatow[1] has recently pointed out that the deposit of the doubly refracting so-called fluid crystals, most abundant in the rabbit, does not take place in all animals. It would seem from the observations on our dogs, that, though the cholesterin content of the blood-serum may be high, there is nevertheless no permanent deposit of cholesterin in the organs, and it is probable that there is a rapid elimination.

It is noteworthy, also, that the acid-fed dogs showed numerous sudanophil droplets in the early stages of the sclerotic hypertrophy; but that these sudanophil bodies had almost, if not entirely, disappeared by the time the fully formed sclerotic area had developed.

The livers of all the dogs, as well as the adrenals, were crowded with sudanophil bodies. It could be shown that there was no fatty degeneration, but merely an overcrowding of the cells, and even to some extent of the intercellular tissue, with an infiltration of fatty material. Doubly refracting components could never be found. The livers of the acid-fed dogs, more than those of any of the other animals, were filled with this fatty substance, and it was especially the cylindrical epithelium of the bile-ducts that was most conspicuously loaded with brilliant sudanophil matter (Fig. 4).

The work is being continued, and definite conclusions would at

[1] Ueber flüssige Kristalle im tierischen Organismus, Frankft. Zeitschrift f. Path., 1911, xiii, Hft. 2, 189.

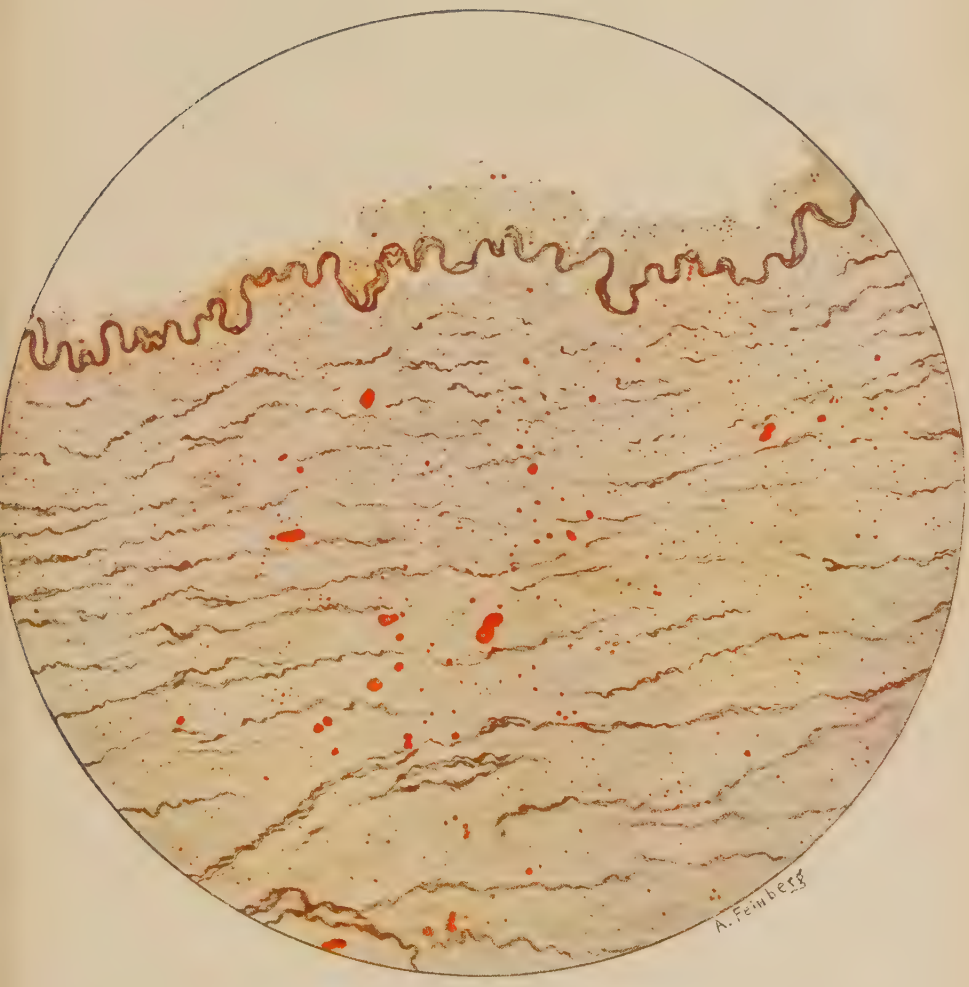
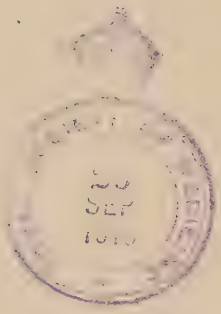


FIG. 3.—Frozen section through a yellow patch of the aorta of an oil-fed dog. Sudan III shows incipient proliferation of the endothelium and distribution of sudanophil bodies.



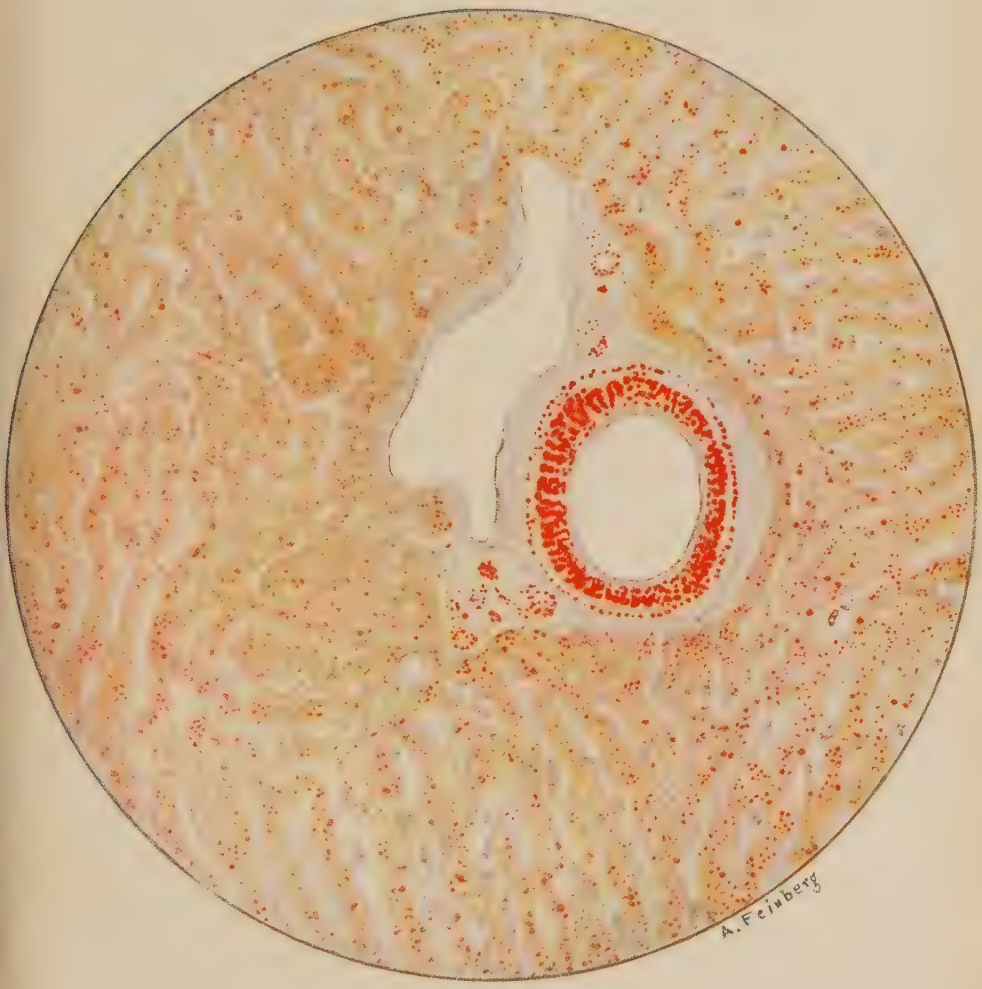


Fig. 4.—Frozen section through the liver of an acid-fed dog. Stained with Sudan III. The liver cells and especially the cells of the bile ducts are crowded with sudanophil bodies.

this stage be premature; but perhaps it may be permitted, even now, to venture the statement that in all probability the theory which bases atherosclerosis on a purely mechanical etiology will not prove tenable. Whether mechanical factors come into play at all, and, if so, to what extent, remains to be seen.

It seems almost certain, at least in our present state of knowledge, that chemical influences subject possibly to more or less nerve control, though this is perhaps venturing too far into the field of speculation, are dominant factors in the etiology of atherosclerosis. Perhaps it may be discovered also that cholesterin and its various modifications and combinations, while undoubtedly an element of great importance in the atherosclerosis of the rabbit and human beings, may not be the sole predominant etiological factor. If it should turn out that so simple a procedure as adding a certain proportion of hydrochloric acid to the food of dogs is sufficient to produce lesions of the bloodvessels closely analogous if not wholly identical with human atherosclerosis, a revision of our present theories will become necessary.

INTRA-UTERINE AMPUTATIONS

By GEORGE DOCK, M.D.
ST. LOUIS

CERTAIN deformities of the extremities, noted at birth, resemble the results of amputations, and it is widely accepted that the process is one of amputation, usually by a loop of the umbilical cord around the affected extremity. Occasional references in medical literature show that the situation is not so simple as would appear at first glance. The site of the amputation is often wrongly conceived, cases like those I now report being sometimes spoken of as amputations in the middle or upper third of the forearm. Moreover the mechanism is by no means simple or obvious in all cases, and further observations, still more, experimental investigations, are needed, and it is in the hope of stimulating more accurate investigations that the following cases are reported.

As regards the literature, (Sir) J. Y. Simpson[1] many years ago wrote an article with full consideration of cases previously reported. Klippel and Bouchet[2] have reviewed the subject very fully in reporting a new case and Joachimsthal[3] has made a valuable roentgenographic study.

CASE I.—S. B., female, widow, aged seventy-seven years, white, admitted to the medical wards of the Washington University Hospital December 13, 1911. The family history, as obtained from the intelligent patient and her niece, is negative, there being no other known anomalies in the generation immediately before or after the patient. There is the

[1] Dublin Jour. Med. Sc., November, 1836, p. 220; also in his Obstetric Memoirs and Contributions, Philadelphia, 1856, ii, 328.
[2] Nouv. iconog. de la Salp., 1907, xx, 290, 396.
[3] Die angeborene Verbildungen der ob. Extremitäten, Hamburg, 1900.

FIG. 1.—Case I.

FIG. 2.—Case I.

common family tradition of maternal impression. When the mother of the patient was in the sixth month of pregnancy she was frightened by a tramp at her door, who had one arm amputated in the way shown later by the infant. Without discussing the subject, it is enough to point out that from the studies of Warren Lewis on the development of the arm[1] the accident was much too late to be considered as bearing on the arrest of development. The right forearm is represented by a stump 2.5 inches long on the flexor, $4\frac{3}{8}$ inches on the extensor surface, the lower end slightly rounded, as in an amputation stump. At the end, on the radial side, is an elliptical area 22 x 25 mm. in diameter, in which five roundish, slightly

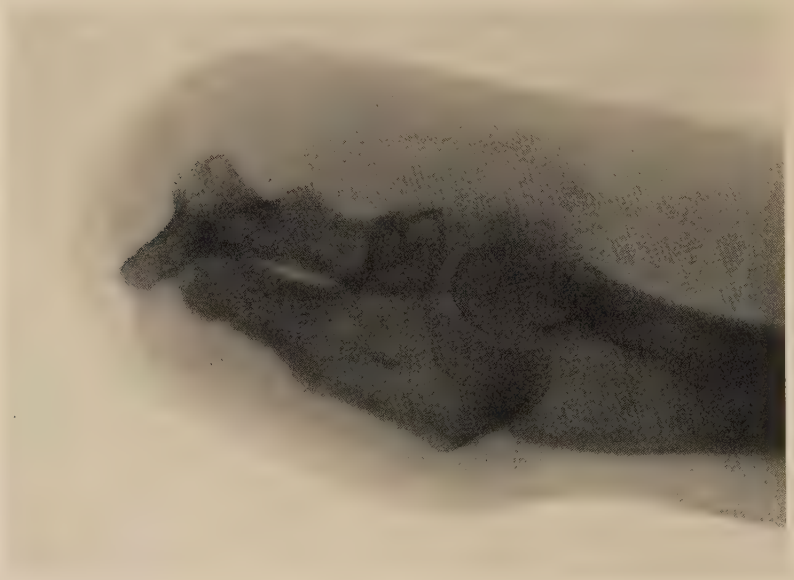


Fig. 3.—Case I.

elevated bodies appear, looking like finger tips. *X*-ray examination shows that the right elbow is well formed. The radius and ulna are present and show remains of the anatomical features of the lower end, especially the styloid process, but the shafts show striking deformities such as have been noted by others. Flexion and extension of the stump are good. The arm is only slightly smaller in bulk than the sound one. The right upper arm measures 13 inches in length, the left $13\frac{1}{4}$. The right is $7\frac{1}{2}$ inches, the left 10 inches in girth, the forearms $7\frac{1}{4}$ and 8 inches re-

[1] Amer. Jour. Anat., 1901 and 1902, vol. i.

Fig. 4.—Case II.

Fig.. 5—Case II.

spectively. The veins and arteries show nothing remarkable; the biceps and triceps of the defective arm are fairly well developed. An effort was made to demonstrate finger marking in the tips, by enlarging photographs, but failed, the skin at the end of the extremity being so callous as to interfere with fine details.

Case II.—In Case II, an out-patient, there is no history of significance. The right forearm is shortened in about the same proportion as in the previous case. At the end is an irregular puckering, as of an amputation with redundant tissue, and with a small oblong elevation at the radial

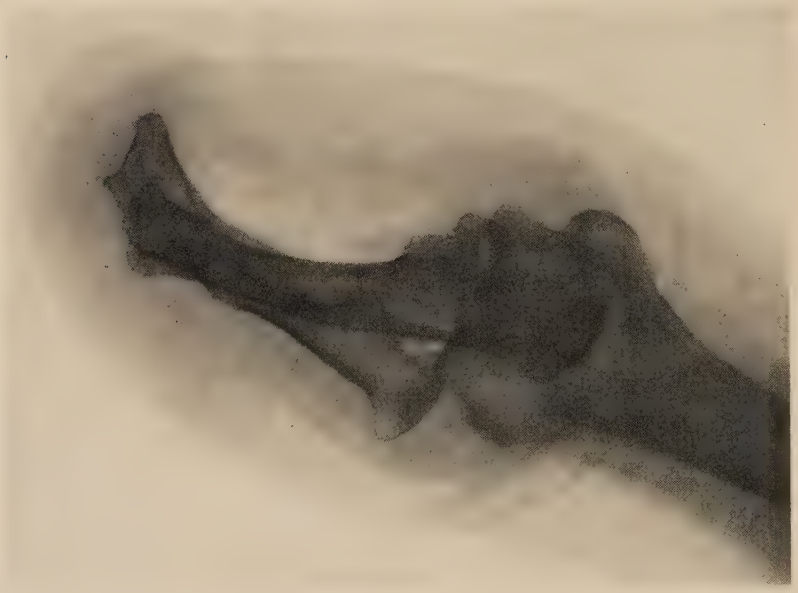


Fig. 6.—Case II.

side. The roentgenogram shows a less perfect elbow-joint, and even more deformity of the radius and ulna than in Case I, but from the distal extremities of this it can hardly be doubted the forearm bones are complete, and the so-called amputation was at the wrist, and not in the middle of the shafts.

Both these cases illustrate deformities in which some rudiments of distal tissue can be seen on the stump. They represent a moderate degree of deformity. In some cases simpler ends occur; in others, rudimentary fingers or toes in normal number or less, and more or

less well developed, are sometimes seen. The mechanism of the latter is obscure. In cases with smooth ends like that of Battle,[1] or with simple scars, there can be little question of amputation, and the question then is how it occurred. Loops of the cord, amniotic bands, constrictions from some other cause, an unexplained gangrene or lack of development from unknown cause, have all been suspected by various observers. In some cases, most of them rather old, remains of fingers, hands or feet have been found in the clots or in the vagina of the mother after birth of the child, or even before. It has been supposed that the rudimentary fingers are the remains of the original ones, but on the other hand, it has been held, especially by M. Duval, that they are due to an effort at regeneration such as is common in starfish.

The amputation has in rare cases been obviously caused by the umbilical cord, generally, however, by bands from the membranes, as shown especially by a case observed by Marchand. The size of the amputated member has some relation to the time of formation of bands, which is most likely to occur between the third week and third month of fetal life.

Other less gross causes cannot be excluded, such as spontaneous gangrene. Examination of the bones in several cases, like my own, show that the bones are not severed in continuity, as has been supposed by many.

The rather frequent association of congenital amputations with supernumerary digits, syndactyly, club foot, cleft palate and spina bifida raises the question whether congenital amputations are in any way under the influence of the endocrinous glands governing bone formation and growth.

DISCUSSION

Dr. Abraham Jacobi, New York: I would like to ask the author of the paper what explanation he gave of those cases that are not amputations of these structures that have finger ends.

[1] New York Med. Record, February 29, 1908, 360.

Dr. George Dock: There are some recent writers who believe it is possible to find fingers regenerated on distal extremities. Another fracture, in the case of an old woman, there was the usual history of maternal impression. Even in these mystical days it would be hard to believe that, and the facts of this case are against that explanation. When the mother was carrying the child, in the eighth month, she was frightened by a tramp coming to the door who had an amputated arm, exactly like the arm we have been speaking about, so there was a tradition in the family, as I got it from an intelligent relative, the amputation was the result of the fright. From a study of the development of the forearm, carefully worked out by Dr. Warren Lewis, such a thing would be quite impossible. The amputation must have happened in this case long before the eighth month, probably soon after the formation of the forearm or about the eighth week.

Dr. Abraham Jacobi, New York: Whenever there is a malformation we must remember that something has happened. The whole explanation of different cases may lie in different directions. I would remind you of cases in which there is a partial giant growth. You have seen cases of giant growth in one finger of the child or an hypertrophy of the side of the face. That can be best explained by the fact that there is a real overgrowth, a real hypertrophy of the growing tissues. On the other hand, those cases it is true, are rare, but all of you have seen probably one or more cases. I saw a giant growth lately of the left cheek in a boy who is now six years of age who is the most advanced of any member in his class; still he has that immense giant growth of his lower and upper jaw. Why not assume in those cases in which limbs are wanting that there is a lack of material, simply under-development. There is not material enough to form the whole length of the limb, perhaps also at the same time some unknown reason why cell proliferation stopped. It would be just as easy to assume in some cases that there is not material enough as it would be to assume that in others there is too much material.

THE INSPIRATORY EXAGGERATION OF THE DICROTIC WAVE IN PERICARDITIS

By ALBERT E. TAUSSIG, M.D.
ST. LOUIS

(From the Department of Internal Medicine, Washington University Hospital, St. Louis)

While taking routine pulse tracings from a case of adherent pericardium, a phenomenon was observed that seemed worthy of further study. With great uniformity it appeared that, during inspiration, the predicrotic notch was accentuated, with a corresponding increase in size of the following dicrotic wave. In all of the cases of pericarditis subsequently seen, whether dry or with effusion, the same phenomenon could be made out. The following is a brief statement of the cases with illustrative tracings:

Case I.—F. S., aged fourteen years, entered the Washington University Hospital, service of Dr. George Dock, March 30, 1912. He showed most of the signs characteristic of adherent pericardium, multiple serositis, pulsus paradoxus, Broadbent's sign, etc., and, at autopsy, the visceral and parietal pericardium were found completely grown together. Throughout the period during which he was under observation the radial pulse showed a marked exaggeration of the dicrotic wave during inspiration. This is well shown by the two accompanying tracings. In Fig. 1, the upper tracing registers the respiratory phases, the up-stroke of the lever marking inspiration, the down-stroke expiration; the lower tracing registers the radial pulse. With each inspiration, the corresponding radial pulses show a marked accentuation of the predicrotic notch and a corresponding increase in amplitude of the dicrotic wave. In Fig. 2 the upper tracing again registers respiration, the lower the radial pulse. It was taken while the patient first held his breath and then resumed respiration. During the apneic period the dicrotic wave was small and did not vary in size. With the first inspiration a marked increase in the amplitude of the dicrotic wave occurred, due apparently chiefly to an exaggeration in the depth of the predicrotic notch.

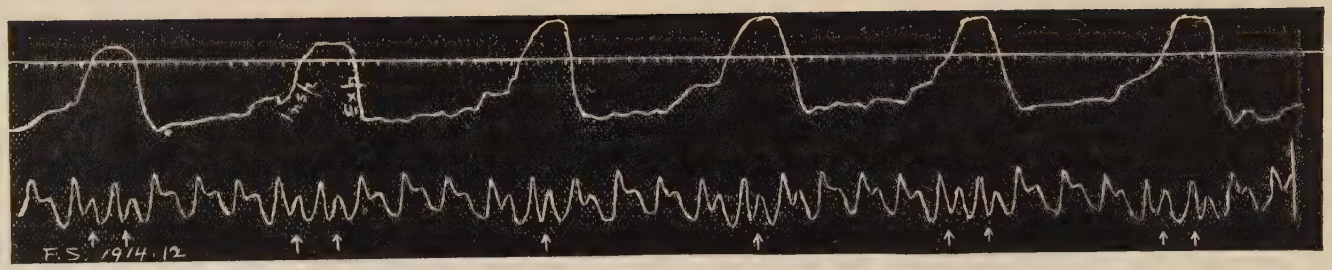


FIG. 1.—Case I. The upper curve registers the respiratory movements, the lower the radial pulse. At points marked with an arrow, the pulse-wave that falls during inspiration is characterized by a deep predicrotic notch and a high dicrotic wave.

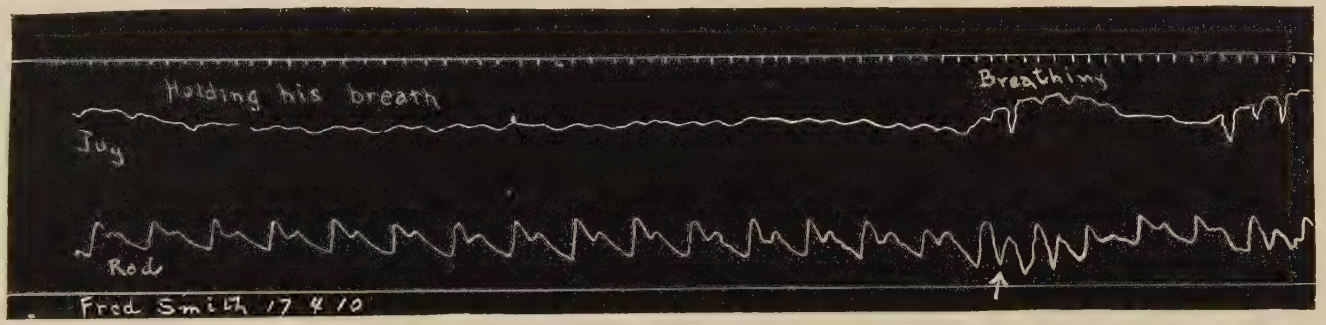


FIG. 2.—Case I. During the first fifteen radial pulses, the patient is holding his breath. At the point marked by an arrow, he takes a deep inspiration. Note the effect upon the radial pulse.

Case II.—B. D., aged sixteen years, entered the Washington University Hospital, service of Dr. George Dock, on December 10, 1912. The clinical picture suggested mitral regurgitation with pericardial effusion. Death occurred before the case could be exhaustively studied. "On opening the pericardium a small amount of turbid fluid escapes. Both walls of the pericardium are glued to each other by an extensive fibrinous exudate."[1]

The tracing (Fig. 3) shows a simultaneous record of the apex beat and the radial pulse. The sudden fall in level of the former marks the inspiration, the rise in level the expiration, the constant level a period of apnea. An inspiratory accentuation of the dicrotic wave, less in degree than in the preceding case, but yet sufficiently definite, can clearly be made out.

Case III.—M., aged twenty-five years, was seen at the St. Louis City Hospital, through the kindness of the visiting physician, Dr. John Salter. The case was one of enormous pericardial effusion, large amounts of fluid being repeatedly withdrawn from the pericardium with prompt reaccumulation. In most of the sphygmograms, the pulsus paradoxus was so marked that the radial pulse nearly or quite disappeared during inspiration. On the occasions, however, on which the pulsus paradoxus was not so extreme, the inspiratory accentuation of the dicrotic wave became apparent, as illustrated in Fig. 4. At first sight the radial pulse, especially in the second half of the tracing, looks like a pulsus alternans, with a reverse alternation of the dicrotic wave. This is, however, not the case. More than a score of tracings taken from the patient within a fortnight show that there is no pulsus alternans. Moreover, a closer study of Fig. 4 shows that the apparent alternation is due to another cause. The pulse rate is accurately twice that of the respiration and the alternate smaller pulse-wave, which occurs during inspiration, is an expression of the pulsus paradoxus, so extremely marked on other days. Moreover, in the latter half of the first portion of the tracing, there is sometimes no alternation of the main wave, while at other times the exaggerated dicrotic wave accompanies the taller rather than the smaller pulse-wave. Invariably, however, the increase in the depth of the predicrotic notch and in the amplitude of the following dicrotic wave coincides with inspiration.

Case IV.—T. W., aged twenty-five years, a private case, was studied with the kind permission of the attending physician, Dr. R. H. McBaine. The case was a typical one of dry pericarditis, with a loud to-and-fro friction rub, growing feebler during inspiration. The patient died a few days after

[1] From autopsy protocol.

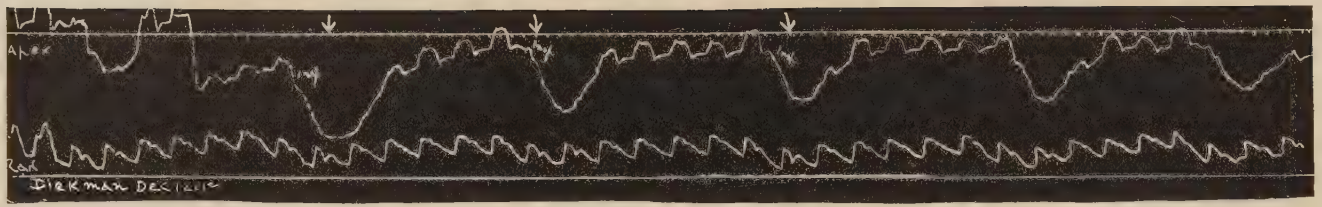


FIG. 3. Case II. The upper curve was taken with the cup over the site of the apex beat, the down-stroke marking inspiration. The arrows indicate the pulse-waves that fall during inspiration and show increased dicrotism.

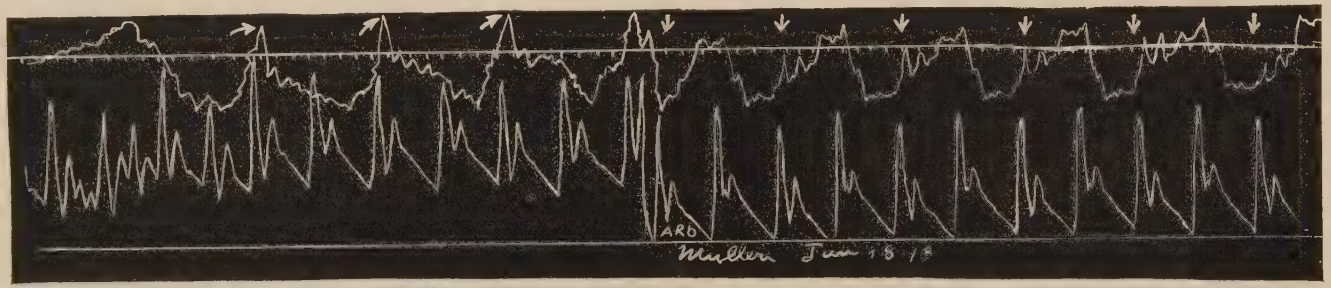


FIG. 4.—Case III. The up-stroke in the jugular tracing marks inspiration. It is during inspiration that the dicrotic wave is exaggerated (arrows). The radial is not a pulsus alternans (see text).

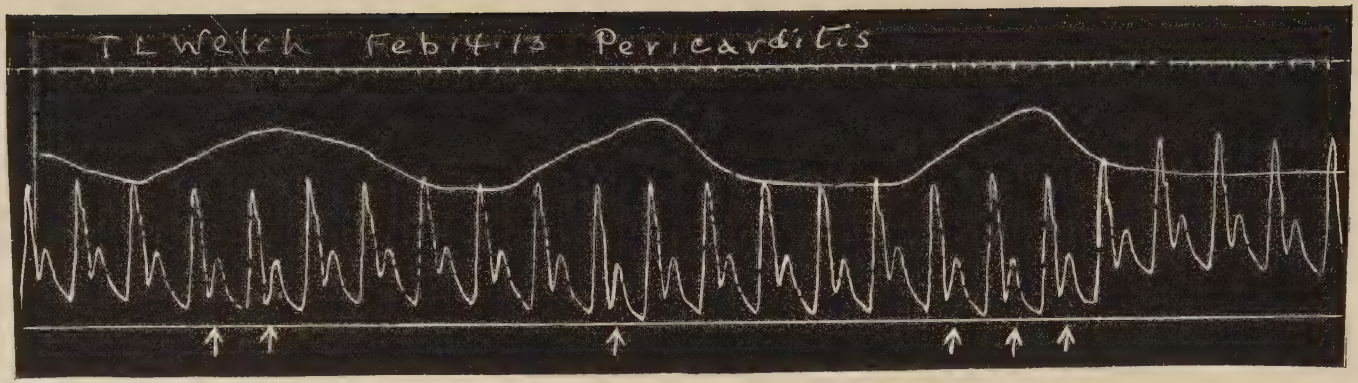


FIG. 5.—Case IV. The up-stroke of the respiratory tracing marks inspiration. During inspiration the altitude of the dicrotic wave increases.

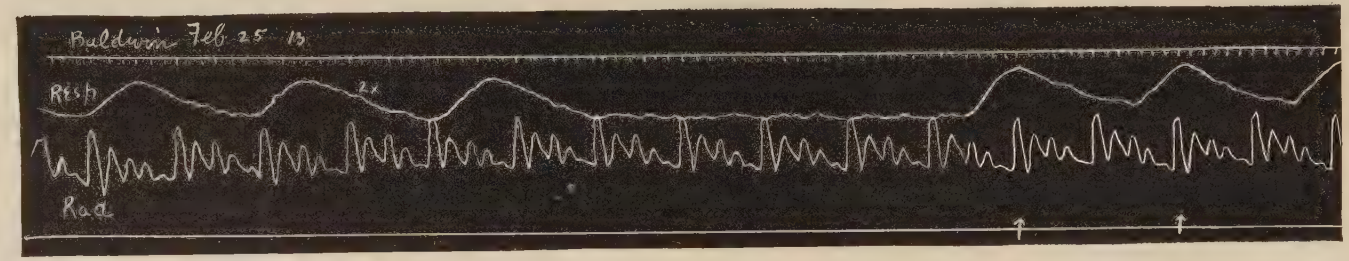


FIG. 6.—Case V. Pulsus bigeminus with marked dicrotic wave. The patient breathed three times, then held his breath. When he resumed breathing, the pulse during each inspiration shows an exaggerated dicrotic wave (arrows).

the tracing was taken; no autopsy permitted. The sphygmogram (Fig. 5) is a simultaneous record of respiration and radial pulse, the former being recorded by means of the usual jugular cup, applied in the right infraclavicular fossa. The up-stroke registers inspiration, the down-stroke expiration. The inspiratory exaggeration of the dicrotic wave is evident.

Case V.—H. B., aged twenty-nine years, entered the Washington University Hospital, service of Dr. George Dock, on February 24, 1912. The diagnosis of this case was by no means certain. There was great pallor, dyspnea; the heart was enlarged both to right and left with the clinical signs of mitral regurgitation and a persistent pulsus bigeminus. Suspicion regarding the presence of pericardial adhesions was first aroused by the presence of inspiratory dicrotism (Figs. 6 and 7). The diagnosis was rendered somewhat more probably by the presence of a definite drawing in of the apex with each systole.

Case VI.—W. L., aged twenty-three years, entered the City Hospital, July 18, 1913, in the service of Dr. O. H. Campbell, who kindly permitted me to study the case. He presented, on entrance, a loud to-and-fro pericardial friction rub, with great precordial pain, and a large left-sided pleuritic effusion. The latter was aspirated several times; the pericardial friction rub gradually disappeared. The *x*-ray plate was strongly suggestive of pericardial effusion, but the single attempt that was made at aspirating the pericardial sack failed to reveal the presence of fluid. In the tracing (Fig. 8), which again records the respiratory phases and the radial pulse, the increase, during inspiration, of the depth of the predicrotic notch, and the corresponding increase in amplitude of the dicrotic wave, while not as extreme as in some of the cases, are nevertheless evident on close inspection.

Case VII.—F. B., aged fifteen years, seen in consultation with Dr. Walter Fischel. In June, 1912, she had what may have been an acute articular rheumatism. In October, edema of the feet set in, and, when first seen by Dr. Fischel in December, she showed marked decompensation with mitral regurgitation. Proper treatment was followed by great improvement, but in October, 1913, a second attack of decompensation set in. When seen in November, the cardiac dulness extended to the left anterior axillary line on the one side and nearly to the mid-clavicular on the other. A soft blowing mitral regurgitant murmur was audible and there was general passive congestion with fluid in the pleural and peritonal cavities. Under strophanthin, she slowly improved, but suddenly died, possibly from an embolus. No autopsy was permitted.

While the possibility of a concomitant pericarditis cannot be denied, there was at no time any definite evidence of the existence of this complication. The case is of interest in our series because

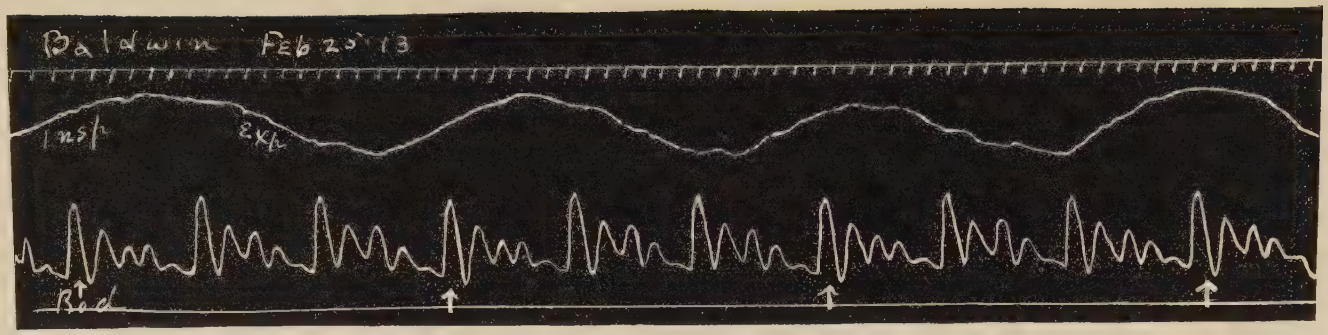


FIG. 7.—Case V. The pulse-waves that begin during inspiration (indicated by arrows), show an increased dicrotic wave.

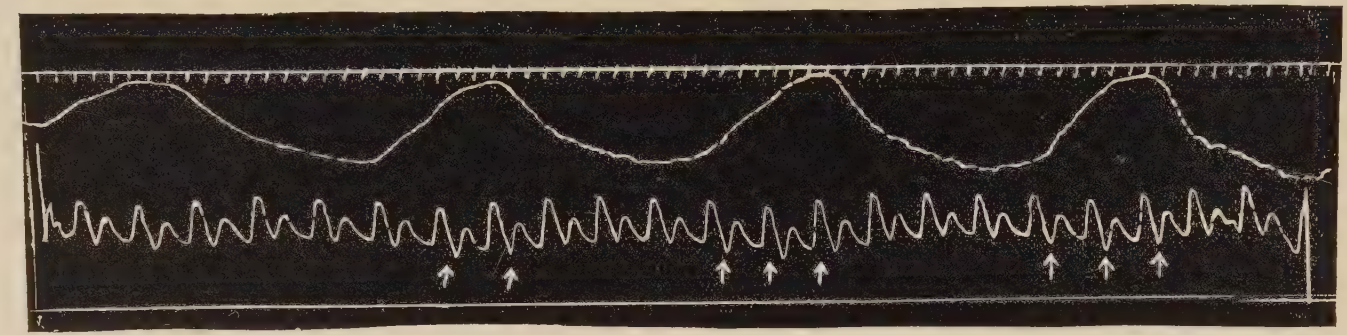


FIG. 8. Case VI. In this case the phenomenon is barely perceptible. Still those pulse-waves whose beginnings fall during inspiration (marked by arrows) have a somewhat more marked dicrotic wave than those whose beginnings fall during expiration. The tracing is chiefly significant as showing that in this case too, the phenomenon was not entirely absent.

the radial pulse (Fig. 9) showed a definite inspiratory increase in the amplitude of the dicrotic wave, here as in the other tracings due chiefly to the increase in depth of the predicrotic notch. Unfortunately the failure to get an autopsy prevents the use of this case either for or against the diagnostic significance of the phenomenon under discussion.

Of these seven cases, the diagnosis of pericarditis is most certain in the first three, being confirmed by autopsy in two (Cases I and II) and by aspiration of fluid in one (Case III). In these three cases the phenomenon under discussion was most marked, being evident at the first glance. In two other cases (Cases IV and VI), the diagnosis was made probable by the presence of what was interpreted as a pericardial friction rub. The first of these two patients was very ill and died soon after the tracings were taken. The latter show a well-marked inspiratory accentuation of the dicrotic wave. The second patient (Case VI) recovered, showing a friction rub for only a brief time. His tracings show the phenomenon only on close inspection. In two other cases (Cases V and VII), the physical findings did not justify the diagnosis of pericarditis, although the presence of this complication could not be excluded. Their tracings show the phenomenon only moderately well. It is for this reason alone that they are included in this series. There seems thus to be a relationship between the extent of the lesion and the degree of variation of the dicrotic wave, the most marked cases of pericarditis showing the phenomenon most distinctly. I have seen no cases of certain pericarditis that failed to show the phenomenon.

The diagnostic value of this phenomenon, if it has any, is impaired by the fact that it is occasionally found in cases in which we have no right to assume the existence of pericardial adhesions or effusion. Usually, however, in these cases, the inspiratory increase in the size of the dicrotic wave is so slight that it can be made out only on close inspection or mensuration of the tracing. Even when it is more strongly marked, it is rarely so pronounced as in cases of pericarditis. Figs. 8 and 9 illustrate the most marked instances of the phenomenon as it occurs in cardiac dilatation, while Fig. 10 was taken from the pulse of a typhoid convalescent.

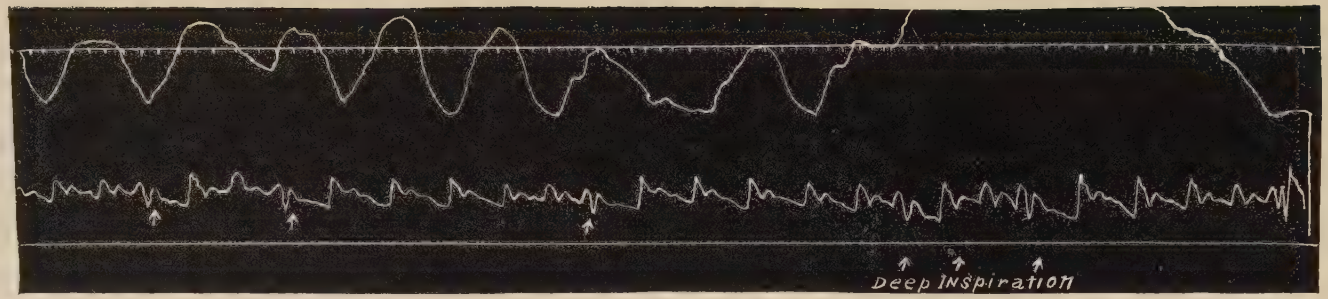


FIG. 9.—Case VII. Inspiration is very short and rapid and comparatively few pulse-beats have their beginning during inspiration. Those that do so are marked with arrows and show a deep predicrotic notch. The case is not a good example of the phenomenon, and indeed the presence of any pericardial lesion was doubtful.

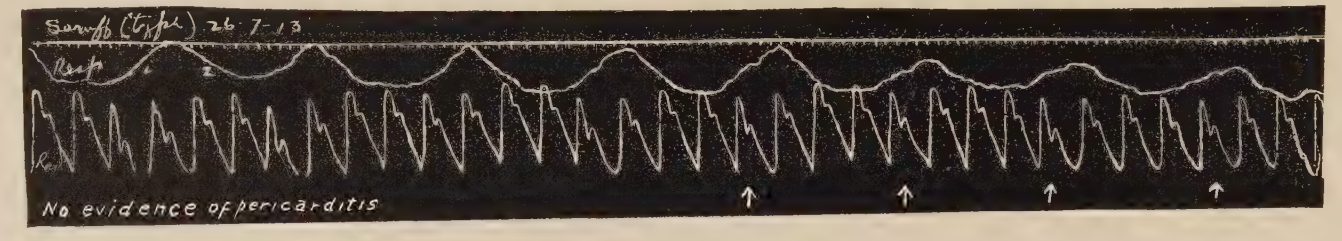


FIG. 10.—Case VIII. Case of typhoid fever without evidence of pericarditis. No other clearly non-pericardial case showed an influence of respiration upon dicrotic wave comparable to this one.

The inspiratory increase in the size of the dicrotic wave was first described by Riegel, in 1876, in connection with his critical study of the pulsus paradoxus. He found both phenomena present, though only to a slight degree, in the pulses of a large number of apparently healthy young people. Sommerbrodt, in the following year, reported even more surprising observations. He found a well-marked pulsus paradoxus present in the majority of healthy people and often as marked as it ever is in cases of pericarditis. He also calls attention to the fact that this pulsus paradoxus is often accompanied by an inspiratory increase in the size of the dicrotic wave. Since both phenomena are present in health, he admits diagnostic significance for neither.

My own observations do not agree with those of Riegel and Sommerbrodt. In tracings taken with the Jaquet sphygmograph, at any rate, neither pulsus paradoxus nor the phenomena described above are commonly observed and, when present, the latter at least is never so marked in other conditions as in pericarditis.

The phenomenon, as it occurs in adhesive pericarditis, may probably be best explained somewhat as follows: After expelling its contents, the left ventricle remains for a brief period in systole. The pressure in the aorta at this moment is high. When the ventricle relaxes, the pressure within its lumen falls far below that in the aorta, just outside the aortic valves. The latter are therefore pushed inward, toward the lumen of the ventricle, as far as they will go. A relative diminution in pressure at this portion of the aorta thus occurs, with a resulting centripetal reflux of blood from the arterial tree. This causes the predicrotic notch. The rebound from the firmly fixed valves produces the dicrotic wave. In all probability the above is only one element in the production of the dicrotic wave, another being the reflection of the pulse wave from the periphery, but it probably plays its part. According to this theory, the occurrence of our phenomenon in the presence of pericardial adhesions, is readily explained. The adhesions more or less firmly fix the heart to the parietes or to the diaphragm. During inspiration the pull outward of these adhesions not only interferes with systole, whence the pulsus paradoxus, but tends to accentuate diastole. When inspiration and diastole occur together, there is

thus an unusually great difference between the intraventricular and aortic pressures, resulting in a maximal pushing inward of the aortic valves, an accentuation therefore of the predicrotic fall of pressure and hence of the following dicrotic wave. In our tracings both of these two last phenomena are equally well marked. In cases of pericardial effusion and still more in the non-pericardial cases, the rationale of the phenomenon is not so clear. Perhaps an unusual flabbiness of the myocardium permitting it to give to the changes of intrathoracic pressure may play a part.

If further observation confirms our results, the increase of the dicrotic wave during inspiration may prove of diagnostic value in cases of pericardial adhesions. Only marked changes in amplitude should, however, be so utilized. Minimal, barely perceptible variations, probably occur in other conditions. Moreover, failure to elicit the phenomenon by no means speaks against the diagnosis of pericarditis. In some of the cases mentioned above the phenomenon was much more marked on some days than on others and occasionally could not be elicited at all. Moreover, it obviously requires a well-marked dicrotic pulse and will thus fail to occur in cases of pericarditis in which this prerequisite is lacking. Such cases have not as yet come under my observation.

In eliciting the phenomenon, the sphygmograph, if the Jaquet apparatus is used, must be so applied that the pelotte rides accurately on the radial artery. The tension on the spring must be rather light and must be so manipulated as to produce a maximum dicrotic wave. With a tension a little too high or too low, the changes in the amplitude of the dicrotic wave may not be recorded even when present to a marked degree.

Summary. An inspiratory exaggeration of the dicrotic wave was observed in seven cases of certain or suspected pericarditis. In four cases the existence of pericardial adhesions was established by autopsy or a well-marked pericardial friction rub. In one other case (Case V) the diagnosis, pericarditis, was probable; in another (Case VII) not impossible. A large number of non-pericardial cases were studied as regards the relationship of dicrotic wave and respiratory phase and no such phenomenon was observed. In the rare cases in which it did occur the change in amplitude of the dicrotic

wave was so slight (not over 0.1 mm.) as not comparable in degree to that found in pericarditis. It may be that the phenomenon is of value for the diagnosis of pericarditis.

It is a pleasant duty to thank my honored chief, Dr. George Dock, for the interest he has shown in this investigation and for permission to report the cases seen in his service.

DISCUSSION

Dr. Henry Sewell: I would like to ask the author of the paper what sphygmograph he used.

Dr. Taussig: The Jaquet instrument.

THE NORMAL AMOUNT OF DIASTATIC FERMENT IN THE URINE AND FECES, AND ITS VARIATION IN DISEASES OF THE PANCREAS

By THOMAS R. BROWN, M.D.
BALTIMORE, MARYLAND

We have studied quantitatively the diastase in the urine and feces in the hope that by establishing the normal limit, especially the low normal, we might have criteria of value in the diagnosis of organic or functional diseases of the pancreas, determining whether or not in such diseases a definite variation from the normal is constantly found. We have chosen the diastase in preference to the trypsin or lipase because of its greater stability, because the trypsin digestion may be simulated by the action of erepsin, because of the marked proteolytic action of the bacteria, much more striking than their diastatic action, because practically all the diastase that is secreted into the intestinal tract arises from the pancreas, the amount from Brunner's glands and gall-bladder, the only other sources, in all probability, being so small in amount as to be practically negligible, because in the case of the urine it is the only ferment, with the exception of pepsin, that is easy to demonstrate, and because it is a preformed ferment and does not require an activator.

We have attempted to devise a method which is simple, practical, and exact, and based on physiological principles, and by applying the same method to normal and pathological conditions to draw comparisons of value in diagnosis. In practically all the diseased conditions the diagnosis was verified by operation, the autopsy *in vivo*.

The Urine. In studying the urine, the earlier studies of which were made alone, the later in conjunction with Mr. C. W. Smith, Jr.,

we used a slight modification of the method first described by Wohlgemuth based on the conversion by diastase of soluble starch (Kahlbaum) into, successively, erythrodextrin, achroödextrin, isomaltose, and maltose, the limit being determined by that tube in which the addition of an iodin solution produces no blue coloration, *i. e.*, when all the soluble starch has been converted into lower products. Wohlgemuth suggested the possibility of using the quantitative diastase estimation as a test of renal function, and, as we shall see later, probably its greatest value is in this connection.

In determining the quantity of diastase in the urine, the twenty-four-hour specimen was carefully collected, and kept under toluol in the ice-box or in a cold place. This was diluted with distilled water to 3000 c.c., and decreasing amounts of this diluted urine were added to a series of tubes.

In our first group of cases we used the method of geometrical progression, that is, 2 c.c. in the first tube, 1 c.c. in the second, 0.5 c.c. in the third, 0.25 c.c. in the fourth, 0.12 c.c. in the fifth, etc., but as the variation between contiguous tubes was too great by this method, we later in our much larger series of cases used the method of mathematical progression, that is, 1.8 c.c. in the first tube, 1.6 in the second, 1.4 in the third, 1.2 in the fourth, 1 in the fifth, 0.8 in the sixth, 0.6 in the seventh, 0.4 in the eighth, 0.2 in the ninth, 0.1 in the tenth, 0.05 in the eleventh, and 0.025 in the twelfth, the last three tubes being, as seen, in geometrical progression.

Each tube was filled with distilled water to 2 c.c., and 2 c.c. of 0.1 per cent. solution of soluble starch added to each tube, incubated for one-half hour in the water-bath at 38° C., rapidly cooled off at the end of that time by nearly filling the tubes with cool water, and by holding the tubes under the cool tap and then quickly tested by the addition of a few drops of $\frac{1}{50}$ normal iodin solution, the limit being the tube just before the first tube in which blue is seen, this limit-tube showing the brown color which erythrodextrin gives with iodin.

Of the 44 normal cases tested (healthy adult men and women), in 4 the limit was tube 8, in 16 tube 9, in 17 tube 10, in 6 tube 11, showing, if one may judge from a series of this size, that the diastase falls within definite limits, these limits corresponding with the dozen cases tested previously by the dilution in geometrical progression.

Expressed in terms of the number of cubic centimeters of 1 per cent. starch converted by the entire twenty-four-hour specimens of urine in one-half hour, calling this our unit, we would have in 4 cases 1500 units eliminated in the twenty-four hours, in 16 cases 3000 units, in 17 cases 6000 units, and in six cases 12,000 units.

This then can be used as our normal, tube number 8 or 1500 units in the twenty-four hours being our low normal. The study as regards the effect of the reaction of the urine upon the ferment showed that this was so slight as to be practically negligible, a slight acidity showing a slight activating effect in comparison with neutrality or slight alkalinity, but not enough to necessitate having the reaction of all specimens the same, as in this great dilution the degree of acidity or alkalinity is extremely slight.

In studying the diastase contents of the urine in pathological conditions in 1 case of diarrhea with fatty stool the limit was tube 9 (3000 units); in 1 case of postoperative gall-bladder fistula with normal pancreas also 9 (3000 units); in 2 cases of chronic pancreatitis with persistent jaundice, the common duct going through the head of the pancreas and being obstructed thereby, the limits were tubes 4 (500 units) and 6 (750 units) respectively; in 1 case of advanced carcinoma of the pancreas with jaundice, tube 1 (333 units); in 1 case of pancreatic cyst, still draining, tube 7 (1000 units); in 1 case no longer draining, tube 10 (6000 units); in 1 case of carcinoma of the esophagus with marked asthenia and emaciation, but a normal pancreas, tube 7 (1000 units); in 1 case of an early carcinoma of the gall-bladder with normal pancreas, tube 9 (3000 units); in 1 case of chronic pancreatitis without jaundice, tube 8 (1500 units). All these diagnoses except the first were verified by operation. Thus it will be seen that in all cases with low readings the patient had either been deeply jaundiced for a long time, which unquestionably deleteriously effects ferment production, although the early effects of bile are distinctly activating, or the disease from which they suffered was one associated with severe ill health and consequent lowering of the bodily functions, and thus none of the findings could be regarded as definitely diagnostic of pancreatic disease, although in some cases suggestive.

Durand,[1] using another method for estimating the urinary diastase, concluded that we should accord to the figures obtained in the urine only a relative value, although both Wohlgemuth and he call attention to the diagnostic value of high urine and low stool readings in the same case as suggestive of pancreatic retention due to stone in the pancreatic duct, etc.

Of course, the two main reasons why the quantitative determination of the urinary diastase is not diagnostic of pancreatic disease are (1) because of the widespread distribution of diastase in the body, and the possibility that in pancreatic disease there may be a vicarious increased diastatic activity of salivary gland and possibly of liver and Brunner's glands and (2) because in renal diseases of various kinds there usually is a marked lessening of the urinary diastase irrespective of the condition of the pancreas and salivary glands due to deficient renal permeability. For these reasons, while a persistently low diastase content in the urine in the presence of normal kidneys is suggestive of pancreatic disease, yet the normal figures in our series are of much more value as a basis on which to study the renal function.

The Stool. The normal readings obtained in the urinary studies not being of special value in the diagnosis of pancreatic disease, we next applied similar methods to the quantitative estimation of the diastase in the stool. Of course, a great many methods have been suggested as qualitative and a few as quantitative tests of the pancreatic function—Sahli's glutoid capsule, Müller and Schlect's gelodurot capsule, the study of the stool for large amounts of meat and fat—creatorrhea and stercorrhea—after the Schmidt diet; the Volhard method of obtaining the duodenal contents from the stomach by administering olive oil by mouth and the examination of the fluid for the pancreatic ferment, Ehrmann's palmitin test, Einhorn's intubation of the duodenum, A. Schmidt's nuclei test, the Cammidge reaction, and the alimentary glycosuria test being among those suggested. None of these is definitely quantitative, however, and for this purpose the estimation of the pancreatic ferment in the stools suggests itself. Of these ferments the trypsin and lipase are more easily destroyed by bacteria, the former is almost similar in action to

[1] Les Procédés d'Examen des Functions du Pancreas, Paris Thesis, 1910.

erepsin, each requires activation to show their maximum efficiency, the former by enterokinase, the latter by bile, and the proteolytic action of the intestinal bacteria may complicate the findings very markedly.

We have, therefore, chosen diastase as the ferment to be estimated, and the fact that it is more stable, that it comes preformed and does not require an activator, and that with the exception of a minimal amount supplied by the secretion from Brunner's glands and the bile its sole source of supply to the intestine is the pancreas, makes it the logical choice. Of course, in all such estimations the salivary diastase—identical in action with that from the pancreas—must be eliminated, but this is easily done by administering a food in liquid form in which the act of chewing is not called into play. Of the other ferments found in the small intestines, erepsin, peptolytic ferment, nuclease, lipase, fibrin ferment, hemolysin, and glucoside—splitting ferment—none appreciably affects the action of the diastase. This action, of course, is the conversion of starch into maltose, the intermediary products being soluble starch, erythrodextrin, achroödextrin, isomaltose, and maltose.

The only justification for an attempt to quantitatively estimate the pancreatic ferments is the fact that many animal and a few human experiments (cases with pancreatic fistula) have shown that there is definite quantitative as well as qualitative response on the part of the pancreas to the quantity and character of the food ingested. Even in 1677 de Graaf studied the action of the pancreas by establishing a pancreatic fistula in a dog, a method subsequently employed by Claude Bernard, who demonstrated the activating effect of ether on the glands' secretion; but it was, of course, Pawlow who demonstrated the fact that there was a definite quantitative relationship between amount and character of food and amount and character of juice, his classical experiments on dogs having been verified by numbers of investigations since. His experiment, such as the one that after 600 c.c. of milk a dog secreted 9 c.c. in the first hour, 7 c.c. in the second, 23 c.c. in the third, 9 c.c. in the fourth, and 2 c.c. in the fifth, and that there was a definite and exact relationship between amount of milk given and amount of juice secreted, should be mentioned in this connection. As to the mechanism of this secre-

tion there has been and still is a considerable difference of opinion. Pawlow believed that it was a nervous reflex through the cortex, Popielski that it was a local nervous reflex through the ganglion cells in the pancreas, while, according to Starling, "the formation of hormones and their circulation through the blood to the reactive tissue suffices to account for the whole activity of the gland, and it is doubtful whether in this activity the nervous system plays any part whatsoever." Of course, according to Bayliss and Starling, this hormone secretion is produced by the action of the dilute hydrochloric acid of the stomach upon the prosecretin found in the duodenal mucous membrane, other acids, acetic, lactic, etc., however, having a similar effect. According to Cohnheim the action of acid upon the duodenum, psychic stimuli, as the smell, taste, or sight of food, and fats, fatty acids, and soaps, all act as stimulants to pancreatic secretion. According to Wohlgemuth[1] the action of the fat is both reflex and humoral, while this same and other observers have proven the activating effect of various other substances upon the pancreatic secretion, such as peptones, alcohol, sodium chloride, lipoids, lecithin, etc. Of special interest is the activating influence of bile upon the pancreatic juice. We have entered into the various views held as to the physiology of pancreatic secretion, as it is of special interest in the interpretation of certain of our findings, notably those in achylia gastrica.

As to the methods described for studying the diastase in the stool to determine the pancreatic function, most are based on the same principle, the conversion of starch into lower products which do not give the characteristic starch reaction with iodin, or the determination of the sugar produced by this cleavage by Fehling's solution or some other reagent. Roberts and Strasburger,[2] Wohlgemuth,[3] Ed. Müller[4] all describe such methods—the results, however, are open to serious criticism, because they used different foods and various or no laxatives, and thus rendered possible enormous variations in the diastase-content of the stool. Diarrhea always increases the

[1] Berl. klin. Woch., 1908, No. 81; Biochemisch. Zeitschr., 1909, xxi, 447, and 1911, xxiii, 303.
[2] Deutsch. Archiv. f. klin. Med., vol. lxvii, p. 24.
[3] Biochem. Zeitschr., 1904, ix, 1.
[4] Zeit. f. inn. Med., 1908, p. 386.

stool diastase, constipation lessens it, while Ury[1] has shown that of the purgatives, senna really increases the diastase in the stool while the bitter waters and bitter salts have no such effect. It would seem wise, therefore, to choose a bitter salt as the laxative of choice in these investigations. Enriquez, Ambard, and Binet[2] and Durand[3] reported a number of cases in which the digestion of starch was measured by the quantitative estimation of the sugar formed and by giving the same diet, milk, the same laxative, sulphate of soda, and by diluting the stool to the same extent minimized the errors inherent in any method not taking these factors into account. We, however, regard the Wohlgemuth test for diastase as far more practical than the quantitative estimation of the sugar formed, and quite as free from criticism on theoretical grounds. As for the results of these quantitative studies, Wynhausen[4] found that in most cases it varied between 500 and 20,000 units; Arnold[5] between 312 and 2000, and Lindeman[6] 200 and over. Rotky[7] thought that the study of the desiccated stool was the only satisfactory method, and that by this method there is not a very great deviation in normal cases. Durand found by the method of Enriquez a variation between 14.2 and 48 units of diastase in the normal stool, the units, of course, being different here from those mentioned above. No discussion of the ferment-content of the stool would be complete without a reference to the very extensive and interesting studies of Crohn in this connection.[8] Although devoting the major portion of his investigations to the study of the duodenal fluid, he has also studied the ferments in the stool. He did not employ cathartics, and used either a fresh night or early morning specimen. In the case of both duodenal fluid and stool he gives a table of normal variations for the three ferments, lipase, trypsin, and diastase, and of these three he believes trypsin is the most constant. He believes that the method lends itself to prognosticating qualitative and quantitative variations in the strength of the pancreatic external secretion.

[1] Biochem. Zeitschr., vol. xxiii, p. 153.
[2] La Semaine médicale, January 13, 1909.
[3] Les Procédés d'Examen des Functions du Pancreas, Paris Thesis, 1910.
[4] Berlin. klin. Woch., 1909, No. 30. [5] Zntralbl. für. i. Med., 1913, xxxiv, 1.
[6] Zeitschr. f. klin. Med., lxxxi, 1 to 2.
[7] Münch. med. Woch., September 30, 1913.
[8] Amer. Jour. Med. Sci., March, 1913.

In the methods employed by us in determining the normal amount of diastase in the stool we have tried to eliminate as far as possible all sources of error, and to so standardize the different steps that mistakes would be reduced to a minimum. The patient was given a high enema the night before, the evening meal being a very light one. At 7 A.M. the next day 750 c.c. of milk were given, at 7.30 A.M., and again at 8 A.M., ½ ounce of Epsom salts ($MgSO_4$), and at 8.30 A.M. a glass of water containing ¼ teaspoonful of bicarbonate of soda. All the stools up to 2 P.M. were saved in a vessel containing two ounces of toluol and kept on the ice or in a cool room. If less than 400 grams or cubic centimeters of stool were obtained an enema of a pint of water was given, as in our experience between 400 and 1100 c.c. of stool was the amount to be expected in the individual case.

Barring the inevitable possible mistakes always associated with the gathering of specimens the possible sources of error are psychic variations in the different patients, differences in their intestinal bacterial flora, and variations in the motor functions of their stomach and intestines, but we believe these inevitable sources of error are reduced to a minimum by the method employed.

The stool was examined as soon as possible, diluted up to 3000 c.c. with normal salt solution, stirred until absolutely homogeneous, a portion centrifugalized for five minutes and the supernatant fairly clear fluid used for the tests.

Diminishing amounts of this fluid were put into a series of tubes, 1.8 c.c. in the first, 1.6 c.c. in the second, 1.4 c.c. in the third, 1.2 c.c. in the fourth, 1 c.c. in the fifth, 0.8 c.c. in the sixth, 0.6 c.c. in the seventh, 0.4 c.c. in the eighth, 0.2 c.c. in the ninth, 0.1 c.c. in the tenth, 0.05 c.c. in the eleventh, and 0.025 c.c. in the twelfth, and the fluid in each of the tubes brought up to 2 c.c. with normal salt solution. If the test showed a negative result in the first tube, or if we suspected very low readings, we used a supplementary series of tubes containing respectively 2 c.c., 3 c.c., 4 c.c. and 5 c.c. of the centrifugalized fecal mixture. To each of the tubes were added 2 c.c. of 1 per cent. solution of soluble starch (Kahlbaum), the tubes were then incubated at 38° C. in a water-bath for one-half hour, cooled by the addition of tap water and by placing them under the cool tap and

tested quickly with a few drops of $\frac{1}{10}$ normal iodin solution, the limit being that tube before the one in which the first definite blue color appears. As in the case of the urine, slight variations in the temperature of the water-bath and slight variations in the reaction of the medium had very slight influence upon the readings, and we therefore did not regard it as necessary to reduce all the specimens to the same degree of reaction to litmus. In a few of our earlier cases the fluid in the tube was reduced in geometrical instead of arithmetical progression. The results obtained in 15 normal adult cases, men and women, being about equally represented (our unit being the digestion of 1 c.c. of 1 per cent. starch solution at 38° C. in one-half hour) were as follows: in three cases, 60,000 units; in 2 cases, 80,000; in 1 case, 100,000; in 7 cases, 120,000; in 1 case, 140,000, and in 2 cases, 240,000. Of course, this means that there was no starch left in the tube corresponding to these units, and the exact figures, of course, would be somewhere between this and the next succeeding tube. The low normal reading in our series, therefore, was tube 10 or 60,000 units. Expressed in the units used by some others, that is the total amount of starch which would be digested by the whole stool (in one-half hour in the water-bath at 38° C.), this would make the limits of our normal readings 600 units to 2400 units, although it is possible that higher figures for the high normal would be obtained if we carried our series of tubes to greater dilutions, but we were specially interested in obtaining a low normal, and this, if one can judge from 15 cases, we have obtained.

Using the same method we have studied a small group of cases of carcinoma of the pancreas and chronic pancreatitis, in most of which the diagnosis was verified by subsequent surgical operation, and also a few cases of achylia gastrica and achlorhydria, some associated with diarrhea and some not.

Carcinoma of the Pancreas. Five cases of carcinoma of the pancreas were studied, three verified by operation and each very extensive, the head of the pancreas being specially involved; a fourth presented the typical picture of the disease, fatty stools of the most marked type, absence of trypsin in the stool (as all the other cases of carcinoma showed, the method employed being the Fuld Casein method), negative results with the Schmidt nuclei test and positive

Cammidge reaction, but this patient was not operated upon, and at her death an autopsy could not be obtained, while the fifth case is still alive and presents a typical picture of the disease. All the cases were advanced cases of the disease—in 4 cases jaundice had been present for a long time, in 1 case no jaundice was seen. In 1 case gall-stones were also found.

In all 5 cases the first tube in our series showed no evidence of starch digestion, and we, therefore, employed supplementary tubes with lower dilutions, 2 c.c., 3 c.c., 4 c.c., and 5 c.c. of the diluted feces being put in each of these tubes respectively, and 2 c.c. of the 1 per cent. starch solution added to each. In each case there was still no evidence of starch digestion in the tube of least dilution (5 c.c. of stool, 2 c.c. of 1 per cent. starch) corresponding to 1200 of our unit (or 12 of the starch gram units employed by some others), and we did not study lower dilutions, as we believed that the limit of error had been reached. Thus in each of these cases we can say that there is practically no diastase in the stool. Wynhausen showed a lessening in one case of tumor of the pancreas; Enriquez, Ambard, and Binet found no diastase in the stool in two cases of cancer of the head of the pancreas, verified by autopsy, and Durand found no diastase in one case of probable carcinoma of the pancreas.

According to modern views, based on the experiments of Wynhausen[1] Wohlgemuth[2] and others, almost all the stool diastase comes from the pancreas, and its absence from the stool is, therefore, very suggestive of some marked disturbance of that organ, probably organic, such as cancer; possibly, although improbably, functional. Complete closure of the pancreatic duct was associated with very weak diastase reaction in the stool, as shown in one case by E. Müller[3] and with no fecal diastase in one case by Durand, and if this obstruction is recent, the urinary diastase shows a marked increase according to Wohlgemuth.

Chronic Pancreatitis. We have made quantitative estimations of the stool diastase in 6 cases of chronic pancreatitis, all verified by operation, a small, hard, definitely diseased organ being found in each case; 3 of the cases showed jaundice of long duration, in these

[1] Berlin. klin. Woch., 1909, No. 30.
[2] Ibid., 1910, No. 3.
[3] Zentralbl. f. inn. Med., 1908, 389.

3 the common duct passing through the head of the pancreas, 3 were not jaundiced, and at operation these cases showed extensive adhesions involving in large extent the right side of the abdominal cavity —involving appendix, cecum, ascending colon, and gall-bladder, and associated with marked constipation; in only one of the 6 cases was there a complete absence of free hydrochloric acid in the gastric contents; one of the cases showed an alimentary glycosuria; one of the cases had gall-stones.

The diastase in the stool in these cases showed, 8000, 7500, 12,000, 8000, 7500, and 3300 of our units respectively—in other words, the presence but the marked diminution in all cases, the highest reading being only $\frac{1}{5}$ of the low-normal. Ehrmann[1] reported a case of chronic pancreatitis with hardening of the head of the organ, with markedly diminished diastase in the stool, and Durand reports 3 similar cases.

It would seem, therefore, that in marked cases of chronic pancreatitis diastase is present in the stool, but in markedly diminished amount. There was practically no difference in the cases with and those without jaundice, thus calling attention to the fact that while jaundice of short duration probably increases the amount of diastase by the activating influence of the bile, as shown by Wohlgemuth[2] nevertheless, the longer action of the bile upon the pancreas is to gradually lessen its functionating activity, as also suggested by certain experiments of ours upon dogs.[3]

Achylia Gastrica and Achlorhydria. We have studied a few cases of achylia gastrica and achlorhydria because of the physiological interest attached to such conditions. If, according to Starling, it is the action of the free HCl upon the duodenal mucous membrane, converting prosecretin into secretin, which alone calls forth the secretion of the pancreas, in the cases of absence of free hydrochloric acid, there should be a marked diminution of pancreatic secretion unless there is a vicarious increased production in the other sources of the ferment (in the case of the diastase this is most improbable, as the minimal amount found in the bile and the very small

[1] Zentralbl. f. inn. Med., 1909, 319.
[2] Biochem. Zeitschr., 1909, xxi, 447.
[3] Johns Hopkins Hospital Bulletin, 1912, xxiii, 263.

amount in the secretion from Brunner's glands represent the only other available sources in the intestines), or in the absence of the usual mechanism, some other form of stimulation is called forth, and in this connection Pawlow's views that a nervous reflex plays a large part in stimulating the pancreas must be given more consideration.

In 6 cases of achylia gastrica a quantitative estimation of the stool diastase was made; three of these cases had persistent diarrhea, the so-called gastrogenous diarrhea; in each of the 6 there was no free and no combined HCl, and the total acid was 12 or less; in three of the cases tested no pepsin was found, the Edestin test being used. Of these 6 cases, in 1 case the stool contained 30,000 units, in 2 cases 60,000 units, and in 3 cases 120,000 or more—in other words, there was no diminution below normal in 5 of the 6 cases, while in 1 case there was only a very slight diminution.

These findings are of interest, in the first place, because they show that in the absence of free hydrochloric acid some other method is employed to call forth the pancreatic secretion, and, in the second place, the diarrhea in some at least of these achylia cases is not due to an associated achylia pancreatica, as O. Gross has suggested, but is probably due to the associated enteritis. Whether the pancreas stimulation is of humoral or nervous origin in these cases or whether both play a part it is difficult to say—the fact that peptone, salt, lipoids, lecithin, and fats can activate the pancreas must be remembered, and in some of these cases, at least, both modes of pancreatic stimulation have been demonstrated. Our results in this connection agree with those of Ehrmann,[1] who studied a similar group of cases by aspirating the stomach after the administration of the Volhard oil meal and testing the fluid obtained for trypsin by the Fuld casein method. His conclusions were that in achylia gastrica and gastric anacidity the function of the pancreas is not harmed but is sometimes even better than normal, and, therefore, to stimulate the pancreas, HCl is not necessary, in fact, it is not the necessary activator of the pancreas as he has shown on dogs with pancreatic fistula; the method is to be regarded more as a qualitative than a quantitative one.

[1] Deutsch. med. Woch., 1909, xxxv, No. 20, p, 879.

As to the etiology of the achylia in our series of cases, carcinoma could be probably excluded in all; in all but one—a young man—the patients were past middle age, and had either defective teeth or pyorrhea alveolaris, or both; in three of the cases a marked splanchnoptosis was present; in two a long alcoholic history, and in only one, a young man, was there a history of prolonged overwork and worry. No case showed that stool suggestive of pancreatic disease—stercorrhea, and it has been our experience that this finding is extremely rare in achylia gastrica.

Our series of normal and pathological cases is a comparatively small one, but the results are very suggestive and warrant further study. In addition to continuing our studies along the lines mentioned in this paper, we are also investigating by the same method the diastase-content of the stool in obstructive and catarrhal jaundice, in diabetes and in hyperchlorhydria and hypersecretion, and if the opportunity arises we will make similar studies in diseases of the adrenal and thyroid glands, the close relationship between these glands and the pancreas being, of course, well known.

Conclusions. From our study of diastase-content of urine and feces in normal and in certain pathological conditions the following conclusions seem warranted in being drawn:

1. In healthy adults the diastase-content of the urine falls within quite definite limits. Markedly small amounts of this ferment in the urine in the absence of renal changes is suggestive, although not diagnostic, of pancreatic disease, but the real value of these normal limits will probably be in furnishing criteria in testing renal function by the diastase output of the urine.

2. The stool, if a rigorously exact method is carried out as to food (milk), purgative employed, preservation of specimen, estimation of ferment, etc., also furnishes a content within definite limits. We cannot insist too strongly upon the procedure being exactly the same in all cases. The effect of waiting too long after the stool has been obtained before making the examination, the influence of variations in temperature in the place where it is kept, and of different laxatives and different foods is so great as to render results obtained by methods in which insistence upon such a rigorous technique has not been made of much less value.

3. Extensive carcinoma of the pancreas showed no diastase in the tube of lowest dilution in our method, and this absence of ferment should prove of great help in the diagnosis of this condition.

4. In chronic pancreatitis diastase is present in the stool, but in markedly diminished amounts.

5. In achylia gastrica the diastase-content of the stool was practically normal in all the cases examined. This, in the first place, suggests that in the absence of hydrochloric acid some other method of pancreas-activation is called into play, and, in the second place, that the diarrhea met with in certain of these cases of achylia gastrica—the so-called gastrogenous diarrheas—is not of pancreatic origin.

6. If all the controllable factors are standardized the results obtained by the study of the diastase-content of the stool should be of real value in the diagnosis of pancreatic diseases and in the study of functional disturbances of this gland.

LIVER FUNCTION AS INFLUENCED BY THE DUCTLESS GLANDS

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In recent publications[1] [2] we have shown that valuable information concerning liver function and liver disease can be obtained by the intravenous injection of a solution of phenoltetrachlorphthalein. The drug is excreted through the bile by the activity of the hepatic epithelium and may be extracted from the feces and estimated with considerable accuracy. The phthalein excretion of normal dogs is quite constant, as is shown by the tables given below. The normal base line curve of phthalein excretion for an individual dog under uniform conditions is still more constant.

We have reported elsewhere[3] experiments that indicate that injury of the liver by means of specific poisons such as chloroform, phosphorus, and hydrazin causes a fall in the phthalein excreted in the feces. The fall in the phthalein curve is proportional to the amount of liver injury and in acute fatal poisoning may reach zero. Given a definite liver injury it is found that a definite amount of the phenoltetrachlorphthalein will appear in the urine, which is free from the drug under normal conditions. Moreover, injury of the liver by actual cautery will cause a definite drop in the phthalein curve, depending upon the amount of injury and inflammatory reaction.

[1] Whipple, G. H., Mason, V. R., and Peightal, T. C., Bull. Johns Hopkins Hosp., 1913, xxiv, 207.

[2] Whipple, G. H., Peightal, T. C., and Clark, A. H., Bull. Johns Hopkins Hosp., 1913, xxiv, 343.

[3] Whipple, Peightal, and Clark, loc. cit.

Under various conditions in which the functional capacity of the liver cell is interfered with, the output of phthalein falls below normal, depending upon the extent of the derangement. For example, in passive congestion of the liver, either experimental or clinical, there will be periods of decreased phthalein output corresponding to the intensity of the stasis or breaks in cardiac activity. The Eck fistula (dog 12-2) provides evidence in the same direction. When the portal blood is shunted around the liver by this means we may not at first get a decrease in liver function, but with the development of liver atrophy and fatty degeneration, a distinct and sometimes a marked depression in the excretion curve will be noted.

It is clear that injury or any definite functional derangement of the liver is associated with a definite change in its excretion of phenoltetrachlorphthalein. Passive congestion and Eck fistula are of especial importance in connection with the experiments given below for they show that a change in nourishment of the liver cell leading to atrophy and perhaps fatty degeneration can be recognized by this functional test.

It is important to recall that shortly after repair of an injury by chloroform or phosphorus the liver may give evidence of hyperactivity and excrete more phthalein than under normal conditions. The same may occur after a small dose of a liver poison, which we may assume acts as an irritant to the liver cells. Young dogs and pups will, as a rule, show a slightly higher excretion than adult or old dogs.

All the evidence suggests strongly that a decrease in functional capacity of the liver is parallel by a lowered phthalein output. May we not assume that a decrease in the phthalein output means a decrease in the functional capacity of the liver? We have studied the liver function in the pathological states brought about by removal of the various ductless glands. The liver function, as indicated by the phthalein excretion is definitely impaired, when the body is suffering from pancreatic or adrenal insufficiency. The liver may show no histological evidence of this change in function, but a constant fall in the phthalein curve occurs which may return to normal if, in the case of partial adrenal extirpation, the remain-

ing fragment undergoes an hypertrophy sufficient for the needs of the body.

After complete pancreatic extirpation there is a steady fall in phthalein excretion which may fall as low as one-third or one-fifth normal. This fact speaks strongly for the idea that pancreatic activity is essential to proper liver function, which is the case with the adrenals; and it contradicts the idea that the pancreas tends to inhibit liver activity, while suggesting that the pancreas may be looked upon as having an accelerating influence on the liver. This may have some relation to recently proposed theories of diabetes.

Hypophysis extirpation may cause fluctuations in the excretion curve—an initial fall and secondary rise. A definite fall occurs shortly before death and is noted before the appearance of subnormal temperatures which may supervene a day or so before death.

Thyroid extirpation causes no change in the excretion curve unless the parathyroids are interfered with. Perhaps in experiments of longer duration we may be able to demonstrate some change in liver function.

Parathyroid extirpation and tetany cause no fall in the phthalein excretion curve, but rather a slight rise above normal. In the last day of fatal tetany the liver function will be normal or slightly above normal, which is remarkable considering the prostration that is present at this time. Also given a falling curve due to pancreas extirpation one can produce a rise in output by parathyroidectomy and tetany, a fact which speaks in favor of the supposition that the parathyroid glands exert directly or indirectly inhibitory action upon the liver.

When we recall the amount of injury that must be done to the liver to cause a definite fall in the phthalein excretion curve, it is obvious what marked influence the adrenals and especially the pancreas must exert upon the liver. It is more than possible that this derangement in liver function may be an important factor in the symptom complex of ductless gland insufficiency.

Method. The method employed has been described in detail in an earlier publication,[1] but some points will be reviewed here. The tetrachlor-

[1] Whipple .Peightal, and Clark, loc. cit.

phthalein solution used for the injections was made up in 100 to 200 c.c. lots in 2.5 per cent. strength, as it was found that such a solution does not precipitate within a couple of weeks if kept in a dark place. The method of preparation has been previously described.[1] This solution for injection was standardized with great care against a known solution containing 10 mg. of tetrachlorphthalein to the liter. This insures the injection of 100 or 200 mg. at each injection and makes for constant excretion. The experiments were done in groups using from three to six dogs of which one normal animal served as a control. The solution was injected using a glass syringe and needle in the jugular vein. Injections were usually made about noon and on the following morning a purge of magnesium sulphate insured complete evacuation of the phthalein-containing feces. A second collection must be made to insure complete evacuation of the drug, but will usually be found to contain only a faint trace, provided the purgation has been satisfactory. It is important to clean the feces from the metabolism cages with great care, using a wash bottle and spatula. It is essential to add about 5 c.c. of alkali to the liter wash bottle, as this shows at once any traces of phthalein which otherwise might be overlooked and helps in the solution of the drug.

The method of extracting the phthalein from the feces may be outlined briefly as follows: The collected feces are diluted to one or two liters including 10 c.c. of strong sodium hydroxide (40 per cent.) and shaken in a machine until a uniform fluid is obtained. One-tenth of this mixture is diluted to 500 c.c. with water and 4 to 5 c.c. of strong sodium hydroxide. Of this 500 c.c. solution, 100 c.c. are taken for precipitation with the calcium solution—calcium chloride 20 per cent. To this 100 c.c. are added 5 to 10 c.c. of the calcium solution, followed by 5 c.c. of strong sodium hydrate and water up to 200 c.c. This effects a final dilution of one-tenth of the feces to one liter, including the alkali and calcium solutions. This solution may be filtered at once and read against a standard phthalein solution containing 10 mg. per liter. The readings will be directly in per cent. if 100 mg. have been injected.

It will be noted that the phthalein excretion in normal dogs is constantly higher than in our last report. This is due to a more accurate method for standardizing the injection solution which in these experiments contained 100 mg. in each 5 c.c. In our earlier experiments the solutions were of constant strength, but the amount of phthalein was overestimated giving a lower excretion in the feces. All these dogs have been injected with the correctly standardized phthalein so that no fluctuations in the curve are attributable to this factor except some of the earlier observations in the first experiment (Eck fistula, dog 12-2) which were made during the year 1912-1913.

[1] Rowntree, L. G., Hurwitz, S. H., and Bloomfield, A. L., Bull. Johns Hopkins Hosp., 1913, xxiv, 327.

Experimental Observations. In all operations the dogs were given morphia before operation and ether anesthesia during the operation, which in no instance lasted more than one hour. The usual aseptic surgical technique was employed and great care exercised in the postoperative treatment to insure a rapid return to normal if possible.

Eck Fistula of Eighteen Months' Duration

Dog 12–2. Black and tan mongrel, female.

Feb. 1, 1913. Ether anesthesia. Eck fistula produced as usual with ligature of portal vein at hilum of liver.

Feb. 3. Dog in good condition; weight 13½ pounds. The dog presented the usual picture seen in successful Eck fistula experiments, having occasional digestive upsets, but in general maintaining normal weight with gradual increase in strength and general activity. Phthalein excretion is shown in the accompanying table, and in part has been recorded elsewhere in an earlier report. The condition has been practically unchanged during the year succeeding the last observation. There were slight fluctuations in the weight curve, but the condition during this time has been uniformly excellent.

June 10, 1914, 12 M. Dog in excellent condition. Weight 16 pounds. Phthalein 0.1 gm. intravenously.

June 11. Urine contains a good deal of phthalein as usual. No feces.

June 12. Abundant fluid feces. Phthalein excretion 45 per cent. 4 P.M. Ether anesthesia and bleeding from femoral. Weight 15½ pounds.

Autopsy. Performed at once. Thorax, heart, lungs, and spleen are all quite normal. Pancreas, kidneys, adrenals, thyroid, and parathyroid all normal. Stomach and intestinal tract normal. Eck fistula shows clean margins and an opening about 3 by 4 mm. The portal vein is completely obliterated at the site of the ligature, and there are no collaterals above this ligature. There are large collaterals in the neighborhood of the kidney, forming easy collateral circulation between the portal and lumbar veins. Liver after bleeding and removal of gall bladder weighs 189 gm. This is to be compared with the normal dog 13-45, weight 15¼ pounds, killed at the same time under the same conditions. Normal liver without gall bladder weighed 232 gm. The Eck fistula liver shows regular lobulation and definite evidence of fatty change. The bile passages are everywhere normal.

Microscopic Examination. Liver shows a remarkable grade of fatty degeneration involving about all of the central two thirds of each lobule. The liver cells contain large droplets of neutral fat and the nuclei stain

sharply. There are no phagocytes nor any evidence of cell necrosis. The marginal third of each lobule is normal. Bile passages and canaliculi are normal. Other organs negative.

Dog 12-2

ECK FISTULA OF EIGHTEEN MONTHS' DURATION

Date.	Phthalein in gm.	Phthalein excreted, per cent.		Weight in pounds.	Remarks.
		Feces.	Urine.		
Feb. 1, 1913	—	—	—	13.5	Eck fistula produced.
Apr. 1	0.10	17	++	15.0	
Apr. 8	0.10	20	0.25	16.0	
Apr. 15	0.10	30	2.0	15.5	
May 26	0.10	36	0.1	17.0	Dog improving.
June 17	0.10	40	0.4	17.0	
July 10	0.10	40	0.9	16.3	
Oct. 27	0.10	34	1.0	15.7	Dog in good condition.
Apr. 27, 1914	0.10	46	0.5	16.0	
June 10	0.10	45	++	16.0	
June 12	0.10			15.5	Autopsy.

The preceding experiment (dog 12-2, Eck fistula) shows several points of interest. A dog can live in health for a year and a half with an Eck fistula. This dog had a liver smaller than a healthy normal dog of the same weight, and the Eck fistula liver was supplied by about one-third the normal amount of blood, yet excreted about two-thirds the normal amount of phthalein. This is a simple example of atrophy and slight fatty degeneration due to decreased or changed blood supply. The dog showed no clinical evidence of liver insufficiency and appeared to be in perfect health, yet this physiological test shows a uniformly subnormal output of phthalein. It must be kept in mind that the mere presence of an Eck fistula does not effect a drop in the phthalein curve which may remain normal for some time after the operation, but the drop in the curve follows when the liver atrophy develops. This comes out in experiments previously reported.[1] Another point of interest in this dog and others of similar type is that pregnancy will not develop. The dogs appear normal in all respects and may go in heat frequently and take the male repeatedly, but no pregnancy follows.

[1] Whipple, Peightal, and Clark, loc. cit.

After the first few weeks when the animals are given plenty of bones and milk with no meat, these animals may be kept indefinitely on the usual mixed diet of cooked meat and bread cakes. They do not stand confinement in cages as well as normal animals, and exercise is needful. These observations bear on the question of operation in liver disease in man, and it seems that a suitable technique for the operation is all that is required before applying the Eck fistula operation successfully to human cases of cirrhosis in which the symptoms of portal obstruction are the dominant ones.

Adrenal Extirpation

Dog 13–56. Young male pup; weight 14 pounds.

Jan. 23, 1 P.M. Phthalein 0.1 gm. intravenously.

Jan. 24. Abundant feces. Phthalein excretion 68 per cent.

Jan. 27, 11 A.M. Ether anesthesia. Right adrenal removed completely. Left adrenal cut across, and the lower pole including about one-third of the gland parenchyma left *in situ*. The upper two-thirds were removed.

Jan. 28. Dog is quite weak, pulse fair, wound dry; weight $12\frac{3}{4}$ pounds. Phthalein 0.1 gm. intravenously.

Jan. 29. Diarrhea marked. Phthalein excretion 44 per cent.

Feb. 3 and 4. Dog improving and quite lively.

Feb. 7, 3 P.M. Dog appears normal; weight $13\frac{1}{4}$ pounds. Phthalein 0.1 gm. intravenously.

Feb. 8. Dog has diarrhea without any purgation. Phthalein excretion 52 per cent.

Feb. 10. Diarrhea continues.

Feb. 21, 12 M. Dog in good condition. Weight $13\frac{3}{4}$ pounds. Phthalein 0.1 gm. intravenously.

Feb. 22. Spontaneous diarrhea. Phthalein excretion 39 per cent.

Feb. 25. Soft feces and fluid stools persisted.

Apr. 8, 1 P.M. Dog in good condition; weight 16 pounds. Phthalein 0.1 gm. intravenously.

Apr. 10. Formed feces. Phthalein excretion 70 per cent.

May 1, 3 P.M. Dog is normal. Operation under ether anesthesia. Left adrenal shows very definite hypertrophy. The fragment is more than double its former size. Fragment cut transversely, the lower half removed and the upper half left intact.

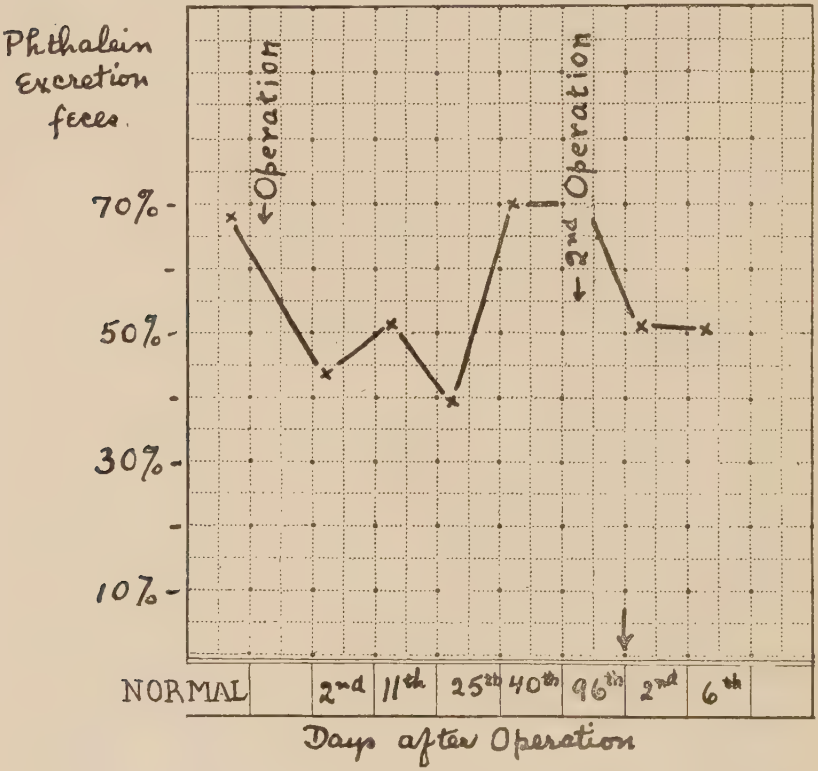
Pancreas. Both upper and lower arm of gland extirpated, but the parenchyma adherent to the duodenum was left undisturbed. Probably three-fifths of pancreatic parenchyma were removed and the blood supply to the remainder left undisturbed.

May 2. Dog in good condition.

May 3, 12 M. Dog appears normal. Wound is dry. Weight 16 pounds. Phthalein 0.1 gm. intravenously.

May 4. No feces. Urine contains no sugar. 5 P.M. Fluid feces. Phthalein excretion 52 per cent.

May 6. Dog vomits occasionally, but has no diarrhea; weight $16\frac{3}{4}$ pounds. Phthalein 0.1 gm. intravenously.



TEXT-FIG. 1. Dog 13–56. Adrenal extirpation.

May 7. Abundant fluid feces. Phthalein excretion 51 per cent.

May 17. Dog appears quite sick and suffers from dyspnea. Temperature 35° C.

May 18. Found dead.

Autopsy. Performed at once. The striking thing is the general anasarca. There is marked subcutaneous edema and accumulation of clear yellow fluid, about 300 c.c. in the peritoneal cavity, and almost the same amount

in the thorax. The pericardial cavity is clear. Heart contains no clots. It shows dilatation and hypertrophy of the right side. Lungs show emphysema and small pulmonary thrombi. Spleen, kidneys, and intestinal tract normal. Liver is rather large, and lobules are conspicuous, due to edema. Pancreatic remnant looks normal. There are adhesions about the sites of operation. Adrenal fragment has increased in size to almost that found at the second operation. Cortex shows very marked hypertrophy. The cause of the general anasarca is quite obscure.

Microscopic Examination. Adrenal gland removed at second operation shows the hypertrophy and increase in fat described by Crowe[1] in a recent publication. The adrenal fragment examined at autopsy shows the same picture together with a certain amount of necrosis, probably dependent upon interference with the blood supply. The parenchyma cells in places look much degenerated. There was undoubtedly a good deal of interference with the adrenal parenchyma and probably a marked insufficiency. The lungs show small patches of organizing pneumonia and induration. Pancreas and kidney are normal. Liver shows central congestion with slight atrophy and fatty degeneration. Some sections show definite central necrosis with thrombosis of adjacent capillaries.

The preceding experiment (dog 13-56, text-figure 1) shows clearly the depression of liver function depending upon adrenal insufficiency. With hypertrophy of the remaining adrenal fragment the liver function returns to normal, as would be expected. The second operation in which one-half of the remaining adrenal fragment was removed was followed by a similar drop in phthalein excretion. At this second operation a portion of the pancreas was removed, but this procedure by itself would have no effect upon liver function. The cause of the anasarca is obscure, but may have been due in part to the changes in the pulmonary circulation causing hypertrophy of the right heart and more or less venous stasis.

The following experiment (dog 13-94) shows that a small adrenal fragment is more efficient in maintaining normal liver function when it is in connection with the sympathetic system by means of its nerves. Furthermore, a simple section of the large nerves going to this upper pole and no interference with the blood supply caused a depression in the phthalein curve when the first operation and removal of three-fourths of the gland parenchyma had given no evidence of insufficiency.

[1] Crowe, S. J., Bull. Johns Hopkins Hosp., 1914, xxv (in press).

Adrenal Extirpation. Nerve Section

Dog 13–94. Small fox-terrier, male; weight 13 pounds.

Mar. 20, 12 M. Phthalein 0.1 gm. intravenously.

Mar. 21. Abundant feces. Phthalein excretion 69 per cent.

Mar. 28, 11 A.M. Operation under ether anesthesia. Right adrenal removed completely. Left adrenal cut across leaving the upper two-fifths of the gland intact, the lower three fifths being removed.

Mar. 29, 11 A.M. Dog in fair condition. Phthalein 0.1 gm. intravenously.

Mar. 30 and 31. Abundant feces. Total phthalein excretion 71 per cent.

Apr. 8. Dog very active; weight 13 pounds. Phthalein 0.1 gm. intravenously.

Apr. 9. Abundant feces. Phthalein excretion 74 per cent.

Apr. 25, 12 M. Operation under ether anesthesia. Left adrenal exposed with very little bleeding and no interference with the blood supply. The large nerve bundle to the upper pole was isolated and cut. The adrenal was handled very little and only this large nerve disturbed. Duration of operation about thirty minutes, which was about half the time required for the first operation, and there was much less handling of viscera during this second operation.

Apr. 26, 11 A.M. Dog is lively and appears normal in all respects. Weight $13\frac{1}{4}$ pounds. Phthalein 0.1 gm. intravenously.

Apr. 27 and 28. Abundant feces. Total phthalein excretion 59 per cent.

May 3, 12 M. Phthalein 0.1 gm. intravenously. Weight $13\frac{1}{2}$ pounds.

May 4. Abundant feces. Phthalein excretion 72 per cent.

June 11. Dog normal. Weight 15 pounds. Ether anesthesia and bleeding from femoral.

Dog 13–94

ADRENAL EXTIRPATION (PARTIAL)

Date.	Phthalein in gm.	Phthalein excretion in per cent. in feces.	Weight in pounds.	Remarks.
Mar. 20	0.10	69	13	
Mar. 28	—	—		Adrenal extirpation.
Mar. 29	0.10	71		Good recovery.
Apr. 8	0.10	74	13	
Apr. 25				Sympathetic to adrenal fragment cut.
Apr. 26	0.10	59	13.3	Good recovery.
May 3	0.10	72	13.5	
June 11	—	—	—	Autopsy.

Autopsy. Performed at once. Thorax, heart, and lungs are normal. Thymus is large, milky, and soft. Testicles are of adult type. Lymph

glands are not particularly enlarged, nor are the lymph follicles conspicuous in the intestine and spleen. The liver is quite normal. Pancreas, kidney, thyroid and parathyroid are normal. Adrenal fragment has increased considerably in size. On section the cortex and medulla appear to be both involved in this hypertrophy.

Microscopic Examination. Liver is normal. Thymus and lymphatic tissue show considerable hyperplasia. Adrenal shows the usual hyperplasia, especially of the cortex. Other organs normal.

Adrenal Extirpation

Dog A–5. Black mongrel pup, female.

Dec. 8, 1913. Ether anesthesia and operation.[1] Right adrenal removed completely. Left adrenal in large part removed leaving small fragment, estimated at about one-fifth of the gland.

Dec. 9, 12 M. Dog in fair condition; weight 10 pounds. Phthalein 0.09 gm. intravenously.

Dec. 10. Soft feces. Phthalein excretion 17 per cent.

Dec. 16, 1 P.M. Dog greatly improved and quite active, in spite of some loss of weight (9 pounds). Phthalein 0.1 gm. intravenously.

Dec. 17. Soft feces. Phthalein excretion 24 per cent.

Dec. 18. Much fluid feces. Phthalein negative. Dog appears prostrated. Pulse is very weak. Temperature 33.5° C. 4 P.M. Death.

Autopsy. Gastritis, which may have been associated with purgation. Other organs normal. Adrenal fragment had undergone the usual hypertrophy. Liver and bile passages are quite normal.

Adrenal Extirpation

Dog 13–107. Strong mongrel pup, female; weight 19¾ pounds.

Apr. 8, 1 P.M. Phthalein 0.2 gm. intravenously.

Apr. 9. Abundant feces. Phthalein excretion 74 per cent.

Apr. 20. Ether anesthesia and operation. Right adrenal extirpated with the exception of a tiny bit of parenchyma at the upper pole, less than one tenth of the substance of the gland. Blood supply much interfered with. Left adrenal extirpated leaving the lower one fourth *in situ*. The blood supply to this fragment was also somewhat interfered with. A good deal of bleeding and handling of viscera.

Apr. 21. Dog looks well, but pulse is weak and rapid. Diarrhea present. Temperature 37.5° C.

Apr. 22, 12 M. Dog in fair condition; weight 18 pounds. Temperature 38.2° C. Phthalein 0.2 gm. intravenously.

Apr. 23. Fluid feces. Phthalein excretion 28 per cent. Dog refuses food and given milk by stomach tube. 3 P.M. Death.

[1] This operation was performed by Dr. S. J. Crowe.

Autopsy. Performed at once. The peritoneal cavity shows a little peritonitis at the site of operation, consisting mostly of fibrin, and there is no free fluid. Adrenal fragments show considerable edema and obvious necrosis, but some parenchyma seems normal. Liver and bile passages are normal. In this animal the adrenal insufficiency was close to the lowest possible limit.

The two preceding experiments (dogs A-5 and 13-107) show the remarkable depression of liver function that may be present in dogs that have almost the minimum necessary adrenal parenchyma. Both these dogs were close to this line of minimum adrenal tissue and the last dog might well have survived but for the peritonitis, which was too much for the animal in this condition of grave adrenal insufficiency. Such a drop in liver function to one-third normal is found only in severe hepatic injury by poisons which, like chloroform, may destroy one-half or more of the liver epithelium. This brings out the paralyzing effect of this adrenal insufficiency upon the liver cells which are quite normal histologically.

Pancreas Extirpation

Dog 13–20. Mongrel pup, male; weight $11\frac{1}{2}$ pounds.

Apr. 19, 11 A.M. Phthalein 0.1 gm. intravenously.

Apr. 20. Phthalein excretion 59 per cent.

Apr. 23, 12 M. Ether anesthesia and operation. Pancreas completely extirpated, with clean dissection along the duodenum.

Apr. 24. Pup is active and lively. Weight $10\frac{3}{4}$ pounds. Phthalein 0.1 gm. intravenously.

Apr. 25. Abundant feces. Phthalein excretion 45 per cent.

Apr. 26, 11 A.M. Dog in good condition; weight $10\frac{1}{2}$ pounds. Phthalein 0.1 gm. intravenously. This caused no appearance of phthalein in the urine.

Apr. 27. Abundant soft feces. Phthalein excretion 24 per cent.

Apr. 28. Dog rather drowsy and eats but little.

Apr. 29. Urine contains a large amount of sugar. Dog is losing weight steadily (9 pounds). 11 A.M. Phthalein 0.1 gm. intravenously. 4 P.M. Urine contains phthalein 3.5 per cent.

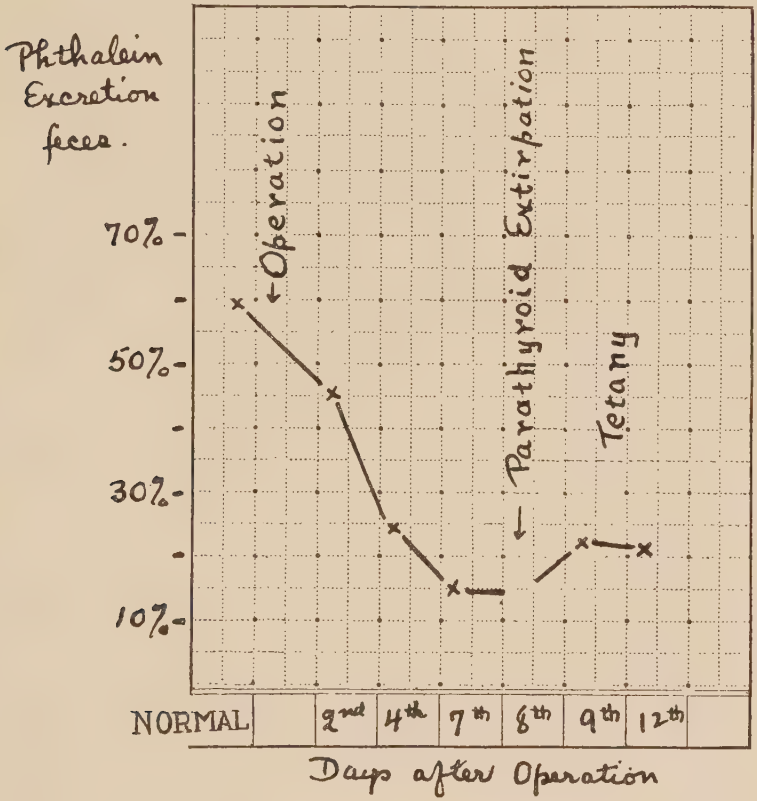
Apr. 30. Much feces with diarrhea. Phthalein excretion 15 per cent. 3 P.M. Ether anesthesia for twenty minutes. Thyroid and parathyroid glands removed completely.

May 1. Dog refused food and given milk by stomach tube. Feces are fluid and slightly blood tinged. There is definite evidence of tetany, mus-

cular twitchings being in evidence in the neck. 11 A.M. Phthalein 0.1 gm. intravenously.

May 2. Dog is dull and drowsy. Small amount of feces. Phthalein content 22 per cent.

May 4, 9 A.M. Dog in poor condition. Temperature 39.5° C. Phthalein 0.1 gm. intravenously.



TEXT-FIG. 2. Dog. 13–20. Pancreas extirpation.

May 5, 9 A.M. Dog found dead. Some fluid feces in cage containing 17 per cent. phthalein. Urine contained no phthalein but some bile pigment.

Autopsy. Performed at once. Intestinal contents as well as gall bladder analyzed for phthalein. 4 per cent. found, making a total phthalein output in about twenty hours of 21 per cent., which is about equal to or slightly more than that of May 2. Lungs show a little bronchopneumonia in lower lobe. Adrenals show a slight atrophy of the cortex. Spleen is rather

small, because of interference with the vascular supply at the time of operation on the pancreas. The liver is very fatty, suggesting the picture of phosphorus poisoning.

Microscopic Examination. Liver cells about the portal spaces for a distance of one or two rows appear normal. Those in the center of the lobule contain great numbers of small fat droplets, but the nuclei are well preserved. No cell necrosis and no wandering cells in the capillaries. Adrenal cells contain a great amount of fat, but appear normal (text-figure 2).

Pancreas Extirpation

Dog 13–98. Yellow adult, male; weight 13½ pounds.

Mar. 19. Ether anesthesia and operation, with complete removal of pancreas, except a few small lobules close to the duodenum.

Mar. 20. Dog appears well. 12 M. Phthalein 0.1 gm. intravenously.

Mar. 21. Urine contains sugar, but no phthalein.

Mar. 22. Abundant feces, phthalein excretion 58 per cent. 12 M. Dog in good condition; weight 12½ pounds. Phthalein 0.1 gm. intravenously.

Mar. 23. Catheterized urine contains no phthalein but considerable sugar.

Mar. 24. Much feces. Total phthalein excretion 56 per cent. 4 P.M. Phthalein 0.1 gm. intravenously.

Mar. 25. Abundant fluid feces. Phthalein excretion 65 per cent.

Mar. 28. Condition unchanged; weight 13 pounds. 3 P.M. Phthalein 0.1 gm. intravenously.

Mar. 29. Abundant feces. Phthalein excretion 46 per cent.

Apr. 16. Dog in poor condition and much emaciated; weight 8½ pounds. 11 A.M. Phthalein 0.1 gm. intravenously. 4 P.M. Urine contains phthalein 1.2 per cent.

Apr. 17. Abundant feces. Phthalein excretion 44 per cent.

Apr. 18, 12 M. Ether anesthesia and operation with complete removal of thyroid and parathyroid glands. Anesthesia twenty minutes.

Apr. 19, 11 A.M. Dog shows signs of tetany; weight 9 pounds. Phthalein 0.1 gm. intravenously.

Apr. 20. Abundant feces. Phthalein output 50 per cent. Typical signs of tetany present.

Apr. 21, 12 M. Condition remains the same; weight 9 pounds. Temperature 37.2° C. Phthalein 0.1 gm. intravenously. 4 P.M. Urine contains phthalein 1.9 per cent.

Apr. 22. Dog in violent tetany. Abundant soapy feces. Phthalein excretion 55 per cent. 4 P.M. Death.

Autopsy. Performed at once. Thorax, heart, and lungs negative. Total absence of subcutaneous and visceral fat. Kidneys normal. Adrenals are rather small, with atrophy of the cortex. Pancreas: there are a few tiny

beads of parenchyma close to the duodenum and pylorus. The liver shows no evidence of fat. It looks rather atrophic. The lobules are regular and normal in color.

Microscopic Examination. The adrenal glomerular zone is narrow. Fat is inconspicuous in the cells. The liver shows slight central congestion. The liver cells show distinct atrophy, somewhat similar to that seen with the Eck fistula. Fatty change is not conspicuous. Phagocytic endothelial cells containing pigment are present in the capillaries.

Dog 13–98

PANCREAS EXTIRPATION

Date.	Phthalein in gm.	Phthalein excretion per cent. in feces.	Weight in pounds.	Remarks.
Mar. 19 . .	—	—	—	Pancreas extirpation.
Mar. 20 . .	0.10	58	13.5	
Mar. 22 . .	0.10	56	12.5	Sugar in urine.
Mar. 23 . .	0.10	65	13.5	
Mar. 28 . .	0.10	46	13.0	
Apr. 16 . .	0.10	44	8.5	Dog emaciated and weak.
Apr. 18 . .	—	—	—	Thyroid, parathyroid extirpation.
Apr. 19 . .	0.10	50	9.0	Tetany present.
Apr. 21 . .	0.10	55	9.0	Tetany marked.
Apr. 22 . .	—	—	—	Death.

The two preceding experiments (dogs 13-20 and 13-98) show the same drop in phthalein output after pancreatic extirpation. The fall in the phthalein curve is much more marked when the pancreas removal is complete. Given this fall in phthalein curve due to pancreatic insufficiency, the onset of parathyroid tetany will cause a distinct rise in phthalein excretion. This experiment gives better evidence for the acceleration of liver function during parathyroid tetany than can be gotten in simple cases of tetany which will be discussed later.

Pancreas Extirpation

Dog 13–104. Mongrel black and tan, male.

Mar. 25, 4 P.M. Ether anesthesia and operation. Pancreas removed almost completely. A few tiny bits remain close to the duodenum.

Mar. 26. Dog in good condition.

Mar. 27. Dog doing well. Urine contains much sugar. Weight 14¼ pounds.

Mar. 28. Sugar abundant in urine. Weight 13 pounds. 3 P.M. Phthalein 0.1 gm. intravenously.

Mar. 29. Abundant soft feces. Phthalein excretion 47 per cent.

Apr. 2. Phthalein 0.1 gm. intravenously.

Apr. 3. Abundant feces. Phthalein output 56 per cent.

Apr. 8, 1 P.M. Dog is weak and emaciated. Weight 9½ pounds. 12 M. Phthalein 0.1 gm. intravenously. 6 P.M. Urine contains phthalein 2 per cent.

Apr. 9. Abundant feces, phthalein excretion 32 per cent.

Apr. 10, 2 P.M. Dog in poor condition and very weak. Ether anesthesia and bleeding.

Autopsy. Performed at once. Thorax, heart, and lungs normal. Fat has completely disappeared. All viscera are normal except the pancreas and liver. One tiny nodule of the pancreas close to the duodenum remains. Dimensions 3 by 5 by 1 mm. Liver shows some focal yellow areas and the centers of all lobules are fatty. Elsewhere the parenchyma is brownish and translucent.

Microscopic Examination. Liver resembles closely that of dog 13-98. The cells show a little atrophy and slight fatty degeneration. Large pigmented endothelial cells are found in the bloodvessels. There are a few polymorphonuclears in the capillaries. No necroses.

Thyroid and Parathyroid Extirpation

Dog 13–51. Mongrel adult, male; weight 15½ pounds.

Jan. 17, 12 M. Ether anesthesia and operation; thyroid and parathyroids removed. At the end of the operation intravenous injection of phthalein 0.1 gm.

Jan. 18. Good recovery.

Jan. 19. Muscular tremors definite. Abundant feces. Phthalein output 35 per cent. 12 M. Muscular tremors are more marked; weight 16¾ pounds. Phthalein 0.1 gm. intravenously. 5 P.M. Convulsive seizures.

Jan. 20 and 21. Tremors present but less violent with milk diet. Total phthalein output 60 per cent.

Jan 21, 6 P.M. Phthalein 0.1 gm. intravenously.

Jan. 23, 4 P.M. Total phthalein output 46 per cent. Delay in purgation, which was incomplete until Jan. 24, may explain this in part.

Jan. 24, 6 P.M. Phthalein 0.1 gm. intravenously. Weight 15½ pounds. Dog on milk diet.

Jan. 26. No feces.

Jan. 27. Much diarrhea. Total phthalein output 57 per cent. Dog in violent tetany and the slightest touch causes a violent spasmodic reaction. 5 P.M. Death.

Autopsy. Performed at once. The autopsy showed nothing abnormal except venous engorgement of organs.

Microscopic Examination. Liver normal.

THYROID AND PARATHYROID EXTIRPATION

Dog 13–13. Fox-terrier, male; weight 15¾ pounds.

Nov. 13, 12 M. Phthalein 0.08 gm. intravenously.

Nov. 15. Abundant feces. Phthalein output 45 per cent.

Dec. 23, 12 M. Dog in good condition. Ether anesthesia, and operation. Thyroid and parathyroids removed.

Dec. 24. Muscular tremors are present; weight 10½ pounds. 1 P.M. Phthalein 0.1 gm. intravenously.

Dec. 25. Abundant feces. Phthalein excretion 42 per cent.

Dec. 26. Phthalein 0.1 gm. intravenously.

Dec. 27. Muscular tremors very marked. Dog refuses food; weight 11½ pounds. Abundant feces. Phthalein output 68 per cent.

Dec. 28. Death.

Autopsy. Normal organs throughout.

The two preceding experiments give definite evidence that there is no decrease in liver functional capacity even during the extreme prostration of fatal tetany. The last of the series (dog 13-13) suggests a definite rise above the normal base line. It must be recalled that the feces excretion of phenoltetrachlorphthalein may be very nearly the same whether the drug is injected intravenously or given by stomach tube. This shows how completely the drug is excreted by the normal liver and how little is lost in the transfer from the blood to the bile. One experiment may be cited as illustrative of this point.

Dog 13–125. Young female pup; weight 14½ pounds.

May 6, 4 P.M. Phthalein 0.1 gm. intravenously.

May 8 and 9. Total phthalein excretion 57 per cent.

May 8, 12 M. Phthalein 0.1 gm. given with milk by stomach tube.

May 9, 12 M. Phthalein excretion 60 per cent.

This experiment shows how narrow the margin may be between the normal phthalein excretion and presumably total excretion into the alimentary tract. Other experiments may show a much greater difference.

One of the experiments given below (dog 13-36) gives evidence

of a slight rise in phthalein excretion above normal in periods of mild tetany, as it is clear that this dog suffered at times from parathyroid insufficiency and died in tetany. Better and more convincing evidence that tetany causes an increase in phthalein liver excretion is found in the preceding experiments under pancreatic extirpation (dog 13-20 (text-figure 2) and dog 13-98). With a falling phthalein curve due to pancreatic insufficiency we see a definite rise caused by parathyroid tetany. This rise is noted, although the general condition of the dog is much less favorable than before the removal of the thyroid and parathyroid glands.

From all this data it seems safe to conclude that during tetany there is a tendency towards an increase in phthalein excretion by the liver, indicating an overstimulus and hyperactivity of the liver epithelium.

Thyroid Extirpation

Dog 13–26. Active adult, male; weight 20½ pounds.

Jan. 26, 3 P.M. Phthalein 0.2 gm. intravenously.

Jan. 27. Abundant feces. Phthalein output 65 per cent.

Mar. 21, 11 A.M. Operation with ether anesthesia. Extirpation of both thyroid lobes, one large parathyroid being left at the lower pole on the left side.

Mar. 22. Dog is well; weight 19 pounds. 12 M. Phthalein 0.2 gm. intravenously.

Mar. 23. Dog is normal. No feces.

Mar. 24. No signs of tetany. Abundant feces. Total output of phthalein 63 per cent.

Mar. 25. No muscular tremors. Weight 19¼ pounds. Appetite good. 12 M. Phthalein 0.2 gm. intravenously.

Mar. 26. Abundant feces. Phthalein excretion 63 per cent.

Apr. 16 11 A.M. Dog in normal condition; weight 18¾ pounds. Phthalein 0.2 gm. intravenously.

Apr. 17. Abundant feces. Phthalein output 66 per cent.

June 8. Dog has been in good condition over the entire period since the operation. Weight 20½ pounds. 12 M. Phthalein 0.2 gm. intravenously.

June 9. Abundant feces. Phthalein excretion 67 per cent.

June 11. Ether anesthesia and bleeding.

Autopsy. Performed at once. All the organs are perfectly normal. Neck shows no definite thyroid tissue. One large parathyroid is found and appears to be normal. Liver and bile passages normal.

Microscopic Examination. Liver normal. Two tiny bits of thyroid tissue found in section. The acini contain little colloid and show a cubical type of epithelium. Parathyroid large and normal. Other organs normal.

Dog 13–26

THYROID EXTIRPATION

Date.	Phthalein in gm.	Phthalein excretion per cent. in feces.	Weight in pounds.	Remarks.
Jan. 26 . .	0.20	65	—	
Mar. 21 . .				Thyroid extirpation.
Mar. 22 . .	0.20	63	19.0	No tetany.
Mar. 25 . .	0.20	63	19.3	No tetany.
Apr. 16 . .	0.20	66	18.7	No tetany.
June 8 . .	0.20	67	20.5	Good condition.
June 11 . .	—	—	—	Autopsy.

THYROID EXTIRPATION

Dog 13–36. Active young female; weight 21 pounds.

Jan. 19, 12 M. Phthalein 0.15 gm. intravenously.

Jan. 20. Abundant feces. Phthalein output 56 per cent.

Jan. 23. Chloroform 15 c.c. by stomach tube, causing slight intoxication.

Jan. 24. Dog will eat little food; weight $20\frac{3}{4}$ pounds. 6 P.M. Phthalein 0.2 gm. intravenously.

Jan. 26. Abundant feces. Total phthalein output 19 per cent.

Jan. 28. Condition appears to be normal.

Feb. 7, 11 A.M. Ether anesthesia with removal of thyroid lobes. One parathyroid at left upper pole was left undisturbed.

Feb. 8. Dog appears well, except for slight muscular tremors. 10 A.M. Phthalein 0.2 gm. intravenously.

Feb. 9. Abundant feces. Total phthalein output 70 per cent.

Feb. 12. Dog active and hungry.

Feb. 15. Dog in good condition; weight 22 pounds. 11 A.M. Phthalein 0.2 gm. intravenously.

Feb. 16, 12 M. Abundant feces. Phthalein excretion 66 per cent.

Mar. 18. Dog in good condition, except for a little mange. Weight $21\frac{1}{2}$ pounds. 4 P.M. Phthalein 0.2 gm. intravenously.

Mar. 19. Abundant feces. Phthalein output 52 per cent.

Apr. 16, 11 A.M. Dog in good condition. Weight $19\frac{3}{4}$ pounds. Phthalein 0.2 gm. intravenously.

Apr. 17. Soft feces. Phthalein output 62 per cent.

May 6, 4 P.M. Dog in good condition. Weight $21\frac{1}{2}$ pounds. Phthalein 0.2 gm. intravenously.

May 7. No feces.
May 8. Abundant feces. Phthalein output 53 per cent.
June 1. Dog has developed violent tetany which resists all treatment.
June 2. Death.
Autopsy. Organs showed advanced postmortem change.

Dog 13–36

THYROID AND PARTIAL PARATHYROID EXTIRPATION

Date.	Phthalein in gm.	Phthalein excretion per cent. in feces.	Weight in pounds.	Remarks.
Jan. 20 . .	0.15	57	21.0	
Jan. 23 . .	—	—	—	Chloroform by stomach (15 c.c.).
Jan. 24 . .	0.20	19	20.7	
Feb. 7 . .	—	—	—	Thyroid and 3 parathyroids extirpated.
Feb. 8 . .	0.20	70	18.5	Slight tetany.
Feb. 15 . .	0.20	67	22.0	Good condition.
Mar. 18 . .	0.20	53	21.5	
Apr. 16 . .	0.20	62	19.7	
May 16 . .	0.20	53	21.5	Good condition. No tetany.
June 1 . .	—	—	—	Violent tetany. Death.

The two preceding experiments (dogs 13-26 and 13-36) show that thyroid insufficiency has no effect upon the curve of phthalein liver excretion. During periods of tetany due to removal of too much parathyroid tissue the excretion curve may fluctuate. It is possible that longer periods of observation may bring out a change in hepatic function with complete thyroid removal. Observations on human cases of exophthalmic goitre would be of interest in this connection.

Hypophysis Extirpation

Dog 13–79. Active male pup; weight 15 pounds.
Feb. 18, 11 A.M. Phthalein 0.1 gm. intravenously.
Feb. 19. Abundant feces. Phthalein excretion 70 per cent.
Mar. 20, 12 M. Dog has practically recovered from distemper; weight $12\frac{1}{2}$ pounds. Phthalein 0.1 gm. intravenously.
Mar. 22. Delay in purgation. Phthalein output 63 per cent.
Apr. 20. Ether anesthesia and operation.[1] Removal of hypophysis.

[1] This operation was performed by Dr. A. P. Jones.

Apr. 21. Dog in good condition. Temperature 39.2° C. 12 M. Phthalein 0.1 gm. intravenously. Weight 15½ pounds.

Apr. 22. No feces.

Apr. 23. Soft feces. Phthalein output 52 per cent. Edema of head wound is marked. Temperature 39.2° C.

Dog 13–79

HYPOPHYSIS EXTIRPATION

Date.	Phthalein in gm.	Phthalein excretion per cent. in feces.	Weight in pounds.	Remarks.
Feb. 18 . .	0.10	70	15.0	Young pup.
Mar. 20 . .	0.10	63	12.5	Recovering from distemper.
Apr. 20 . .	—	—	—	Hypophysis extirpation (incomplete).
Apr. 21 . .	0.10	52	15.5	Slight fever.
Apr. 24 . .	0.10	57	15.0	Improving.
Apr. 27 . .	0.10	67	14.7	Good condition.
Apr. 29 . .	0.10	76	15.0	
May 3 . .	0.11	57	15.0	Good condition.
May 8 . .	0.10	52	16.5	
June 8 . .	0.10	61	16.5	Good condition.
June 11 . .	—	—	—	Autopsy. Remnant of anterior lobe.

Apr. 24, 12 M. Dog appears normal; weight 15 pounds. Phthalein 0.1 gm. intravenously.

Apr. 25. Abundant feces. Phthalein output 57 per cent.

Apr. 27, 12 M. Condition unchanged; weight 14¾ pounds. Phthalein 0.1 gm. intravenously.

Apr. 28. Abundant feces. Phthalein output 67 per cent.

Apr. 29. Condition normal. 11 A.M. Phthalein 0.1 gm. intravenously.

Apr. 30. Abundant feces. Phthalein output 76 per cent.

May 3. Condition the same; weight 15 pounds. 12 M. Phthalein 0.11 gm.

May 4. Abundant feces. Phthalein output 57 per cent.

May 8. Good condition; weight 16½ pounds. 12 M. Phthalein 0.1 gm. intravenously.

May 9. Abundant feces. Phthalein output 52 per cent.

June 8, 12 M. Good condition; weight 16½ pounds. Phthalein 0.1 gm. intravenously.

June 9. Abundant feces. Phthalein output 61 per cent.

June 11. Ether anesthesia and bleeding.

Autopsy. Performed at once. Hypophysis absent except a small fragment of anterior lobe at the base of the sella turcica. All other organs

appear normal in all respects. The subcutaneous fat is well preserved. Liver and bile passages are normal.

Microscopic Examination. Liver is normal. Other organs are negative.

Hypophysis Extirpation

Dog 13–74. Active young male; weight 18½ pounds.

Feb. 10, 10 A.M. Phthalein 0.1 gm. intravenously.

Feb. 11. Abundant feces. Phthalein output 66 per cent.

Feb. 17. Ether anesthesia and operation.[1] Complete removal of hypophysis.

Feb. 18. Condition good. 11 A.M. Phthalein 0.1 gm. intravenously.

Feb. 19. No feces.

Feb. 20. Abundant feces. Phthalein output 55 per cent.

Dog 13–74

HYPOPHYSIS EXTIRPATION

Date.	Phthalein in gm.	Phthalein excretion per cent. in feces.	Weight in pounds.	Remarks.
Feb. 10	0.10	66	18.5	
Feb. 17	—	—	—	Hypophysis extirpated.
Feb. 18	0.10	55	18.7	
Feb. 21	0.10	65	20.3	Dog improving.
Feb. 25	0.10	69	18.5	Good condition.
Feb. 28	—	—	—	Convulsions and coma.
Mar. 1	0.10	50	17.0	Subnormal temperature.
Mar. 3	—	—	—	Death. Temp. 31.3° C.

Feb. 21. Dog improving; weight 20¼ pounds. 12 M. Phthalein 0.1 gm. intravenously.

Feb. 23. Abundant feces. Phthalein output 65 per cent.

Feb. 25, 11 A.M. Dog in good condition; weight 18½ pounds. Phthalein 0.1 gm. intravenously.

Feb. 26. Abundant feces. Phthalein output 69 per cent.

Feb. 28. Convulsions and coma, with almost complete absence of pulse, giving the appearance of death.

Mar. 1, 10 A.M. Dog is quite toxic. Temperature 36.8° C. Weight 17 pounds. Phthalein 0.1 gm. intravenously.

Mar. 2. Dog in semistupor. Temperature 36.7° C. No feces.

Mar. 3, 9.30 A.M. Pulse slow. Temperature 31.3° C. Weight 16 pounds. Thin, blood stained feces. Phthalein excretion 50 per cent. 2 P.M. Death.

[1] This operation was performed by Dr. S. J. Crowe.

Autopsy. Performed at once. All organs are normal. Liver and bile passages are normal.

Microscopic Examination. Spleen and lymph glands show slight hyperplasia of lymph follicles. Liver shows acute engorgement of centers of lobules.

Hypophysis Extirpation

Dog H–3. Mongrel female; weight 17 pounds.

Jan. 26. Ether anesthesia and operation.[1] Complete removal of hypophysis.

Jan. 28. Dog in good condition; weight 17¼ pounds. 12 M. Phthalein 0.1 gm. intravenously.

Jan. 29. Abundant feces. Phthalein 41 per cent.

Dog 3

HYPOPHYSIS EXTIRPATION

Date.	Phthalein in gm.	Phthalein excretion per cent. in feces.	Weight in pounds.	Remarks.
Jan. 26 . .	....	..	....	Hypophysis removal.
Jan. 28 . .	0.10	41	17.3	Temperature 39.4° C.
Jan. 31 . .	0.10	62	16.5	Temperature 39.6° C.
Feb. 3 . .	0.10	57	16.0	
Feb. 7 . .	0.10	47	17.3	Dog very drowsy.
Feb. 12 . .	0.10	46	15.5	Distemper mild.
Feb. 16 . .	0.10	40	14.0	Convulsions.
Feb. 17 . .	—	—	—	Death.

Jan. 31. Dog looks sick. Temperature 39.6° C. Weight 16½ pounds. Phthalein 0.1 gm. intravenously.

Feb. 1. Abundant feces. Phthalein output 62 per cent.

Feb. 3. Condition fair; weight 16 pounds. Temperature 39.8° C. Phthalein 0.1 gm. intravenously.

Feb. 4. Abundant feces. Total phthalein output 57 per cent.

Feb. 7. Dog is drowsy. 3 P.M. Phthalein 0.1 gm. intravenously. Weight 17¼ pounds.

Feb. 8. Abundant feces. Phthalein output 47 per cent.

Feb. 10. Dog developed definite signs of distemper.

Feb. 12. Dog is drowsy; weight 15½ pounds. 5 P.M. Phthalein 0.1 gm. intravenously.

Feb. 13. No feces.

Feb. 14. Abundant feces. Phthalein excretion 46 per cent.

[1] This operation was performed by Dr. A. P. Jones.

Feb. 16. Dog in convulsions. Temperature 40.9° C. Weight 14 pounds. 3.30 P.M. Phthalein 0.1 gm. intravenously.

Feb. 17. Dog in stupor; pulse weak. 10.30 A.M. Death. Phthalein in cage and from intestinal contents combined, 40 per cent.

Autopsy. Performed at once. Lungs show ecchymoses and some small patches of bronchopneumonia. Pancreas shows fat necroses with hemorrhage, an example of spontaneous hemorrhagic pancreatitis. Kidneys show small gray nodules in the cortex. Intestinal tract negative. Liver is rather pale and fatty.

Microscopic Examination. Pancreatitis is of considerable age, showing a good deal of scar tissue throughout the gland, although there are some relatively fresh necroses of pancreas parenchyma and fat. The lungs show atelectasis and some bronchopneumonia. The kidneys show accumulations of mononuclear wandering cells in some parts of the cortex. Parenchyma is normal. There is slight atrophy of the liver cells in the center of the lobule. Otherwise normal.

The three preceding experiments are uniform in all respects. Complete removal of the hypophysis will cause little change in the liver function, as indicated by phthalein excretion. There is an initial drop in the phthalein excretion following the operation, and this cannot be attributed to the anesthetic. Possibly the cerebral edema and trauma may account for it. This is followed by a recovery to normal or even a little above normal. Just before the fall in body temperature, which usually precedes death in these dogs, there is a definite impairment of liver function. In the experiment (dog 13-79) in which a bit of the anterior lobe remained, one sees minor fluctuations in the phthalein curve, which may be dependent in part on the hypophysis insufficiency which was undoubtedly present.

SUMMARY. When phenoltetrachlorphthalein is injected intravenously, it is eliminated from the body in the bile through the activity of the hepatic epithelium. The feces may be collected after purgation and the phthalein extracted and estimated against a standard solution. The estimation of phthalein can be done with accuracy in a suitable colorimeter and the elimination in normal dogs is quite constant.

Given a definite liver injury by means of poisons (chloroform phosphorus), the amount of phthalein excreted will be diminished and the fall in output will be proportional to the amount of injury. With an acute fatal poisoning the curve may fall to zero.

Under certain conditions of vascular interference the liver phthalein may show a decreased output; in passive congestion of the liver and with the Eck fistula the liver output may fall considerably below normal.

Known disturbances of the liver function due to parenchymatous injury or vascular disturbances are indicated by a fall in the phthalein excretion curve. Conversely it may be claimed that a drop in phthalein excretion may indicate a decrease in the functional capacity of the liver even if there be no detectable histological changes.

Adrenal insufficiency produced by extirpation of three fourths or more of the gland tissue will be associated with a drop in liver phthalein excretion. With hypertrophy of the adrenal fragment the excretion comes back to normal, but may fall again when more adrenal tissue is removed (text-figure 1).

Pancreatic insufficiency causes a progressive fall in the phthalein excretion indicating a grave lowering of the functional capacity of the liver (text-figure 2). This fact has a direct bearing on the question of diabetes.

Parathyroid insufficiency with tetany causes no decrease in phthalein output, but at times a rise above normal. This comes out best when the phthalein curve is low following pancreas extirpation. Parathyroid tetany may cause hyperactivity on the part of the liver cells.

Thyroid insufficiency produces no change in the uniform curve of phthalein excretion.

Hypophysis insufficiency shows an initial fall in the curve, followed by a return to normal and a final drop in the last few days before death.

These experiments supply evidence to the effect that the liver is very much concerned in the derangement that follows the removal of the ductless glands. Hence it seems probable that this disturbance of the liver function may be an important factor in the general symptom complex of ductless gland insufficiency.

In conclusion we wish to express our appreciation to Dr. S. J. Crowe and Dr. A. P. Jones for assistance rendered in performing some of the operations for gland removal.

STUDIES IN LIVER FUNCTION

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Introduction. This investigation was undertaken to determine (1) to what extent and with what frequency demonstrable functional changes accompany anatomically diseased livers; (2) in what clinical types of liver diseases the functional changes are most marked; (3) whether or not dissociated functional changes occur; and (4) the value and limitations prognostically and diagnostically that attach to these various tests. The objects are two-fold: to ascertain the behavior of the liver in pathological conditions, and to see if the behavior allows of diagnostic and prognostic deductions.

The incompleteness of the information obtained with the usual clinical studies is apparent to every thoughtful clinician. The clinical picture and the anatomical changes do not furnish an accurate conception of the functional condition of the liver nor do they furnish reliable criteria concerning the outcome of these functional changes, nor is there a well-defined symptom complex which can be accepted as the picture of hepatic insufficiency such as exists in relation to certain other viscera, notably the kidney, heart, suprarenals and thyroid. The desire of broadening and deepening our acquaintance with the functional conditions in disease of the liver is apparent and is attested to by a large number of tests devised and introduced for this purpose.

The Function of the Liver in Health. The liver plays an important role in the general nutrition of the body. No anatomical or functional differentiation of liver cells exists, all being identical

as far as can be determined. Three functions of liver cells are definitely established: (1) The glycogenic function, relating to carbohydrate metabolism. This consists of (*a*) the conversion through enzymatic activity of monosaccharides (dextrose, levulose, and galactose) brought to the liver cells by the blood, into glycogen, a polysaccharide closely related to starch; (*b*) the temporary storage of glycogen as such, until (*c*) the reconversion of glycogen by liver enzymes into dextrose as need arises for sugar throughout the body. (2) The formation of urea in relation to nitrogenous metabolism through the activity of the liver cells. This consists in the conversion of certain nitrogenous bodies (NH_3, amino-acids, etc.) into urea, which in turn is carried to the kidneys, where it is excreted. (3) The formation of bile, which is in part an excretion carrying with it waste material and in part a secretion concerned in digestion, playing an important role, particularly in the absorption of fats.

Other functions are frequently ascribed to the liver. Their connection with it, however, is not so well established and they have not played so important a role in the studies of liver physiology. In this group must be considered the formation of fibrinogen and of antithrombin. Undoubtedly still other important functions exist of which at present little or nothing is known.

The Tests of Liver Function. Until recently tests of the functional capacity of liver in disease have been based exclusively on the well known physiological functions of the liver, and have attempted quantitatively or qualitatively to determine its capacity along such lines. In this connection carbohydrate studies first occupied the clinicians, physiologists, and pathologists. The French school led by Roger,[1] Achard and Castaigne, Baylac,[2] Bierens de Haan,[3] championed the sugars as tests of liver function, while the German school under the leadership of Quincke,[4] Frerichs, von Noorden,[5] Kraus and Ludwig,[6] Bloch[7] and Müller were unable

[1] Rev. de Méd., 1886, vi, 935.
[2] Compt. rend. Soc. de Biol., 1897, iv, 1065.
[3] Arch. f. Verdauungskrankh., 1898, iv, 4.
[4] Berl. klin. Woch., 1876, xiii, 529.
[5] Pathologie des Stoffwechsels, 1893, p. 274.
[6] Wien. klin. Woch., 1891, iv, 855.
[7] Ztschr. f. klin. Med., 1893, xxii, 524.

to demonstrate any marked or constant reduction in sugar tolerance in cases of liver disease.

In a series of papers in 1898-1900 Strauss[1] established the view that the discrepancies in the results of these various workers could be explained by differences in the particular carbohydrate employed, together with the differences in the amounts of sugar administered. He followed his criticism of these carbohydrate studies by the introduction of his levulose test, based on the work of Sachs,[2] which showed a constant decreased tolerance for levulose in liverless frogs. His test has come into rather widespread use. Strauss' results as well as those of Ferranini,[3] Landsberg,[4] Chajes,[5] v. Halasz,[6] Hohlweg,[7] v. Frey,[8] Churchman,[9] Falk and Saxl,[10] Bruining,[11] being tabulated in our recent paper. It appears that the test is far from satisfactory and that little reliance diagnostically or prognostically can be placed in its findings.

In 1906 Bauer[12] introduced galactose as a test of liver function laying particular emphasis on its value in cases of catarrhal jaundice. This has been confirmed by Bondi and König,[13] Reiss and Jehn,[14] and Hirose.[15] Falk and Saxl,[16] v. Frey, and Hirose have demonstrated that the findings of the test are very inconstant in diseases of the liver other than catarrhal jaundice.

Before the International Congress of Medicine in 1913, Strauss[17] reported a comparative study in which levulose and galactose were both employed—levulose 100 gm. and galactose 30 gm.—in which he showed that the levulose gave a positive finding more than twice as often as the galactose. He advises the above doses for a com-

[1] Berl. klin. Wchnschr., 1898, xxxv, 398; 1899, xxxvi, 159; Deutsch. med. Wchnschr., 1901, xxvii, 757.
[2] Ztschr. f. klin. Med., 1899, xxxviii, 87.
[3] Zentralblatt f. inn. Med., 1902, xxiii, 921.
[4] Deutsch. med. Wchnschr., 1903, xxix, 563.
[5] Ibid., 1904, xxx, 696.
[6] Wien. klin. Wchnschr., 1908, xxi, 44.
[7] Deutsch. Arch. f. klin. Med., 1909, xcvii, 443.
[8] Ztschr. f. klin. Med., 1911, lxxii, 383.
[9] Johns Hopkins Hosp. Bull., 1912, xxiii, 10.
[10] Ztschr. f. klin. Med., 1911, lxxiii, 325.
[11] Berl. klin. Wchnschr., 1902, xxxix, 587.
[12] Wien. med. Wchnschr., 1906, lvi 20–23.
[13] Ibid., 1910, lx, 2617.
[14] Deutsch. Arch. f. klin. Med., 1912, cviii, 187.
[15] Deutsch. med. Wchnschr., 1912, xxxviii, 2, 1414.
[16] Ztschr. f. klin. Med., 1911, lxxiii, 131 and 325.
[17] Proceed. Seventeenth Internat. Cong. Med., 1913, Sect. V, Part II, p. 395.

parative study. From his collective review of the literature it appears that in normal individuals 15 per cent. of positive findings, in congested livers 17 per cent., in cirrhosis 83 per cent., in icterus in early stages of lues 75 per cent., in obstructive jaundice 62.5 per cent., and in tumors 38 per cent. positives have been obtained with his levulose test.

Bloomfield and Hurwitz,[1] studying lactose tolerance in $CHCl_3$ and phosphorus dogs, feel that little value in relation to liver function can attach to studies of tolerance of any sugar.

Urea, Amino Acid, and NH_3 Nitrogen of Urine. In 1907 Glaessner[2] showed that in most instances of liver disease an unusually high excretion of NH_2N occurred and that the ratio of NH_2N to total non-proteid nitrogen was increased. Subsequent work by Falk and Hesky,[3] Falk and Saxl, and v. Frey indicates that a knowledge of the urinary N is important, and that liver insufficiency is characterized by a decreased percentage of urea N and increased percentage of NH_3N and NH_2N. Levene and Van Slyke[4] and Yoshida[5] each reported two cases of liver cirrhosis in which a normal NH_2N per cent. of the total nitrogen was found.

Urobilinogen. As early as 1892 the presence of urobilinogen in the urine was considered as indicative of disease of the liver by v. Jaksch.[6] Neubauer[7] demonstrated that Ehrlich's[8] p. dimethyl-amino-benzaldehyde test given by certain urines is really a test of urobilinogen. This is the test which has been generally employed. The work of Münzer,[9] Münzer and Bloch,[10] Fischler,[11] Bauer,[12] Falk and Saxl indicates that urobilinogen occurs in the urine in many forms of liver disease. The recent thorough and comprehensive study of the question of urobilinogen by Wilbur and Addis[13] shows conclusively that observations on a single or a twenty-four-

[1] Johns Hopkins Hospital Bull., 1913, xxiv, 375.
[2] Ztschr. f. exper. Path. u. Therap., 1907, iv, 336.
[3] Ztschr. f. klin. Med., 1910, lxxi, 261.
[4] Jour. Biol. Chem., 1912, xii, 301. [5] Biochem, Ztschr., 1909, xxiii, 239.
[6] Klinische Diagnostik, 1892, 3 Aufl., 348.
[7] Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol., München, 1903.
[8] Berl. med. Wchnschr., 1901, No. 15.
[9] Med. Klin. (Berl.), 1913, ix, 586.
[10] Arch. f. Verdauungskrankh., 1911, xvii, 260.
[11] München med. Wchnschr., 1908, lv, 1421.
[12] Zentralbl. f. inn. Med., 1905, xxvi, 833.
[13] Arch. Inter. Med., 1913, xiii, 235.

hour specimen have no significance, since tremendous variations occur from day to day, and that only where repeated observations are made over a period of at least two weeks, and then only where control studies of the urobilin contents of the feces have been made to exclude blood destruction as a factor in the production of urobilinogen, can its findings be accepted. The discussion of Hildebrandt's urea paper before the International Congress by v. Noorden[1] and by Müller,[2] together with a consideration of the work of Wilbur and Addis, indicate clearly how futile are deductions based on urinalysis alone.

The basis for each of these tests is some well-recognized physiological function of the liver. Other tests have been recently employed empirically or because reasons have been recently adduced indicating their connection with liver function.

Fibrinogen. Following the observations of Doyon and Kareff[3] and Nolf[4] that the fibrinogen disappeared from the blood after liver extirpation, and of Doyon[5] and his school that decreased content occurred in chloroform poisoning, and of Corin and Ansiaux[6] and of Jacoby in phosphorus poisoning, Whipple[7] and his co-workers developed a quantitative method which they have applied in studies of the fibrinogen content of the blood in health and disease, in clinical and experimental conditions. Their findings in acute and chronic liver injury make it reasonably certain that the liver is very active in the formation of fibrinogen and is the most important factor in maintaining a constant fibrinogen balance. Therefore, a study of fibrinogen content of the blood has been undertaken in this investigation.

Lipase. In 1913, Whipple, Mason and Peightal[8] utilizing Loevenhart's technique, demonstrated that the lipolytic activity

[1] Proc. Seventeenth Internat. Congress of Medicine, Sect. VI, Part II, p. 55.
[2] Ibid.
[3] Compt. rend. Soc. de Biol., 1904, lvi, 612.
[4] Arch. intern. d. Physiol., 1905, iii, 1.
[5] Compt. rend. Soc. de biol., 1905, lviii, 30; Doyon, Morel, and Billet, Compt. rend. Soc. de biol., 1905, lviii, 108.
[6] Jahresb. u. d. Fortschr. d. Thier. Chemie, 1894, xxiv, 642.
[7] Whipple and Hurwitz, Jour. Exp. Med., 1911, xiii, 136; Whipple, Arch. Int. Med., 1912, ix, 365; Whipple, Mason, and Peightal, Johns Hopkins Hosp. Bull., 1913, xxiv, 207.
[8] Johns Hopkins Hosp. Bull., 1913, xxiv, 207; Whipple, Peightal, and Clark, Johns Hopkins Hosp. Bull., 1913, xxiv, 343; Whipple, Amer. Jour. Physiol., 1914, xxxiii, 50.

of the blood varied from normal in certain diseases of the liver. Severe experimental injury to the liver resulting from chloroform, phosphorus and hydrazine always produced increase in plasma lipase from two to eight times the normal. Clinically Whipple found an increased lipolytic activity in several cases of eclampsia, invariably so in those showing hemorrhagic portal vein necrosis, in pneumonia, peritonitis, leukemia and in the early stages and sometimes in the late stages of cirrhosis. The lipolytic activity of the blood in pernicious vomiting, uremia, jaundice, and obstructive jaundice, was normal. He therefore concludes that high lipase values will be found in practically all cases of eclampsia, liver injury with necrosis due to poisons, intoxications or infections, acute yellow atrophy, cholangeitis, and abscess of liver with considerable destruction of liver tissue.

Phenoltetrachlorphthalein. Simultaneously, clinical studies by Rowntree, Hurwitz and Bloomfield[1] and experimental studies by Whipple, Peightal and Clark were carried on to determine whether the excretion of this drug through the intestines in health and disease afforded information relative to liver functional capacity. Whipple's studies revealed the facts that in chloroform and phosphorus poisoning marked decrease in the phthalein output resulted, together with the appearance of the drug in the urine, and, further, that associated with the decrease in phthalein output decrease in fibrinogen and increase in blood lipase occurred. The clinical studies, 80 determinations on 67 patients, showed that a normal could be established and that many liver injuries, particularly of severe grades, were associated with a decided decrease in the phthalein putput.

Fibrinolytic Ferment. Dr. Goodpasture, of the pathological staff, was already interested in the presence of a fibrinolytic ferment in the blood in liver cirrhosis when this work was undertaken. Samples of blood from all our patients were submitted to him for study. Through his courtesty we present the results of his studies on this series of cases. The ferment is specific for fibrin, does not attack fibrinogen, and is destroyed by heating to 65° C. Details of his studies will appear shortly.

[1] Johns Hopkins Hosp. Bull., 1913, xxiv, 327.

Regimen. In order to obtain comparable results an attempt was made to have the patients under conditions as identical as possible. The patients were kept in bed and on the ward cardiac diet. That the diet was not the same is indicated by the difference in the amounts of urinary nitrogen excreted—some of the patients eating all the food given to them, while others apparently ate but little. Following the ingestion of the phthalein one or two compound cathartic pills were given, depending upon the ease with which the individual responded to purgation. No metabolic studies with determination of nitrogen balance were made.

Methods. Phenoltetrachlorphthalein. This test was employed according to the technique described by Rowntree, Hurwitz, and Bloomfield. The methods for preparing the solution, administration, collection of materials for study and determining the amount of phthalein excreted are given in full in their publication.[1] The only point of variation has been in the employment of 0.8 per cent. NaCl instead of H_2O in diluting the dye prior to injection. In many instances 8 c.c. of the dye have been injected directly with the syringe, no dilution being made.

Fibrinogen. The heat coagulation method as described by Whipple[2] was used in these determinations. It is as follows: Clear plasma, obtained from the oxalated blood, was measured into a centrifuge tube and heated in a water bath at 58° to 60°, for twenty-five minutes. The precipitate was collected by centrifugalization, washed thoroughly with cold and hot water and alcohol, with repeated centrifuging, washed into a weighed Gooch crucible with alcohol, washed with alcohol and ether, and dried to constant weight at 110° to 115°. This method has been carefully studied by Whipple and has been shown to give constant results and has been controlled by the plasma-serum coagulum method. However, where the fibrinogen content is very low, the method may give slightly too low values.

Lipase. This determination can be made either on oxalated plasma or serum, there being little difference in the results, except that the serum lipase is slightly higher owing to the dilution of the

[1] Rowntree, Hurwitz and Bloomfield, Loc. cit.
[2] Amer. Jour. Physiol., 914, xxxiiii, 501.

plasma by the oxalate. All our estimations have been made on plasma lipase with the exception of two or three cases, where serum was utilized. Loevenhart's[1] method of determining the lipolytic activity was utilized. The technique is as follows: Four tubes are prepared, each containing 1 c.c. of plasma and to each is added 4 c.c. of distilled water and 0.3 c.c. of toluol. To two of the tubes is added 0.26 c.c. of ethyl butyrate, the other two serving as controls. The tubes are stoppered and shaken and incubated at 38° for eighteen to twenty-four hours. They are now titrated to neutrality with $\frac{N}{10}$ acid and $\frac{N}{10}$ alkali using azolitmin as indicator. The controls show the titrable blood alkalinity to be about 0.1 c.c. $\frac{N}{10}$ acid. The ethyl butyrate tubes give the amount of acid production above the neutral point and the sum represents the total acid production or lipolytic activity.

The Total Non-protein Nitrogen, Urea Nitrogen, and Amino Acid Nitrogen of the Blood. Blood serum has been used in these analyses unless otherwise stated. Ten to 15 c.c. of serum were mixed with nine volumes of 95 per cent. ethyl alcohol,[2] allowed to stand twenty-four hours or longer, and filtered through a dry paper, 10 c.c. of this filtrate, corresponding to 1 c.c. of serum, were used for the estimation of the total non-protein nitrogen by the micro method of Folin and Denis.[3] However, instead of removing the ammonia from the digestion mixture with the use of the air current, it was distilled[4] from a small flask into 1 c.c. of $\frac{N}{10}$ hydrochloric acid, made up to 50 or 100 c.c. in a graduated flask, Nesslerized, and compared with a standard solution of pure ammonia sulphate containing 1 mg. nitrogen per 100 c.c. in the Rowntree and Geraghty's modification of Autenrieth-Königsberger colorimeter. The remainder of the alcoholic filtrate was evaporated to dryness, and used for an amino acid determination by Van Slyke's[5] nitrous

[1] Amer. Jour. Physiol., 1902, vi, 331.

[2] At first we used acetone, methyl alcohol and zinc chloride to precipitate the free proteins (Folin and Denis, Jour. Biol. Chem., 1912, xi, 527), but since zinc chloride apparently precipitates some amino acids (Van Slyke, Jour. Biol. Chem., 1913, xvi, 187), we changed to the simpler procedure of using only ethyl alcohol. A few comparative determinations with methyl alcohol and zinc chloride and ethyl alcohol alone gave practically the same value for the non-protein nitrogen.

[3] Jour. Biol. Chem., 1912, xi, 527.

[4] This modification willl be described shortly by Dr. B. B. Turner.

[5] Jour. Biol. Chem., 1912, xii, 399.

acid method. The correction for urea and amines other than α-amino acids was always determined and appropriate correction made. The urea was determined by Marshall's[1] method, utilizing soy bean urease for the hydrolysis of the urea.

The Total Nitrogen, Urea, Ammonia and Amino Acids in the Urine. All determinations were made on a complete twenty-four-hour specimen, which had been collected under toluene. The total nitrogen was estimated by the usual Kjeldahl-Gunning method, the urea by Marshall's[2] method, and the ammonia by Folin's[3] method. In the amino acid determination in urine the free amino nitrogen was determined. Any increase in the conjugated amino nitrogen should also be evident from this determination and disturbing effect of albumin is here obviated. Van Slyke's[4] method was utilized, of which the technique is as follows: 25 c.c. of the urine were treated with 10 c.c. of an extract of soy bean urease and 5 c.c. of water. This was digested at 38° until the decomposition of the urea was complete, and then made up to 50 c.c. with a 10 per cent. suspension of calcium hydrate. The mixture was filtered, and 20 c.c. of the filtrate evaporated to dryness in a Jena glass dish. The residue was moistened with acetic acid, diluted to 10 c.c. and 2 c.c. used for an estimation of the amino nitrogen in the micro-apparatus.[5] A blank with 25 c.c. of 1 per cent. urea solution instead of urine was always run as a control and appropriate correction made. The slight correction for other amines not α-amino acid was neglected as it is very small and constant[6] and would not at all influence the results. The figures obtained represent the free amino nitrogen in 2 c.c. of the original urine.

Galactose. Bauer's galactose test was performed as follows: 30 grams of galactose as advised by Strauss[7] are administered to the patient in the morning, and the urine collected for the next five to six hours. The presence or absence of galactose in the urine was determined by Fehling's test. No quantitative studies of the amount excreted were made.

[1] Jour. Biol. Chem., 1913, xv, 487.
[2] Ibid., xiv, 283; xv, 495.
[3] Zeitschr. f. Physiol. Chem., 1902, xxxvii, 161.
[4] Jour. Biol. Chem., 1913, xvi, 125.
[5] Van Syke, Ibid., 121.
[6] Ibid.
[7] Loc. cit.

Levulose. One hundred grams of levulose are administered in the morning, and the urine voided during the following five to six hours tested by Fehling's and Seliwanoff's tests for the presence or absence of levulose. Considerable difficulty was experienced with the performance of this test owing to nausea and vomiting following the consumption of such large amounts of sugar.

Normal Limits of Each Test. *Phenoltetrachlorphthalein* injected in twenty-four cases in which the livers were believed to be normal showed an excretion from 30 to 53 per cent. The average output in afebrile cases was 37.4 per cent., while that in the febrile class was 39 per cent. The lower limit of normal is, therefore, considered 30 per cent. for forty-eight hours. In health following the injection of 400 mg. of the substance, phthalein is practically never encountered in the urine. In cases of clinical or experimental liver lesions the excretion of the phthalein in the urine as well as bile is a common occurrence.[1]

Fibrinogen. Whipple[2] in a series of thirty observations of the fibrinogen content of normal dogs found variations from 200 to 867 mg. per 100 c.c. Individual fluctuation is very large even in a short space of time. However, in human cases no such wide variation was noted. In a series of approximately normal cases the fibrinogen varied between 385 to 618 mg. per 100 c.c. We have placed the lower limit of normal at 350 mg.

The normal *lipase* values for human plasma determined by the above method correspond to an acid production of 0.2 to 0.35 c.c. of $\frac{N}{10}$ acid. Owing to some difficulty in titrating the mixtures and frequent variation of 0.05 or even 0.1 c.c. in duplicate determinations, we feel that no significance is to be attached to values (chloroform or phosphorus poisoning) the lipolytic activity of the lower than 0.4 c.c. In experimental liver lesions in animals plasma is always increased, and frequently reaches values of 1 c.c., 2 c.c., or even greater.

The *total non-protein nitrogen, urea N*, and *amino acid N* of the blood or the relations existing between these constituents have never been utilized in connection with studies on liver function.

[1] Rowntree, Hurwitz, and Bloomfield, loc. cit.
[2] Amer. Jour. Physiol., 1914, xxxiii, p. 56.

The fact that the liver is generally considered as being the organ mainly concerned with the formation of urea, and the metabolism of amino acids led us to make these determinations in this connection. In a series of sixteen strictly normal individuals Folin and Denis[1] found the total non-protein nitrogen to be 22 to 26 mg., and urea N, 11 to 13 mg. per 100 gm. of whole blood. As soon, however, as one goes from the strictly normal, wide variations occur. Out of 63 cases of syphilis only 13 showed normal values, the variations being 20 to 45 mg. of total non-protein nitrogen, and 10 to 26 mg. of urea N. Our experience has been similar to this, and in papers on kidney function we have not regarded values below 50 mg. for total non-protein nitrogen and 25 mg. of urea N per 100 c.c. serum as of any diagnostic or prognostic import. Determinations of the amino acid content of the blood either in health or disease are practically lacking. Van Slyke and Meyer[2] found in dogs the amino acid N of the whole blood between 3.1 to 5.4 mg. per 100 c.c.

In considering what one should regard as normal in this connection, it seems fairer to work with hospital or dispensary patients who give no evidence of kidney or liver disturbance. We have made these three blood determinations on a series of such cases, the results being tabulated below.

TABLE I

Clinical diagnosis.	Mgm. per 100 c.c. serum.			Of T. N. P. N.	
	T. N. P. N.	Urea N.	NH_2 N.	Urea N per cent.	NH_2 N per cent.
Chronic urethritis, verumontanitis, prostatitis	32	22	2.8	70	8.2
Chronic urethritis	24	12	2.5	50	9.6
Chronic urethritis	28	13	2.8	46	9.3
Bubo	22	10	2.6	45	10.8
Pyelitis	38	16	2.1	50	6.1
Normal	31	16	2.6	52	8.4
Normal	19	9	2.0	47	10.5
Normal	22	9	1.7	41	7.8
Normal	25	11	2.0	44	8.0

We have, therefore, considered anything below 40 per cent. for the urea N as abnormal, and above 3.0 mgm. per 100 c.c. the upper limit of normal for amino N. Of course the series of normals is small, and greater variation may be found to occur in health.

[1] Jour. Biol. Chem., 1913, xiv, 29.

[2] Ibid., 1912, xii, 399.

The output of *nitrogen* in the urine depends primarily upon the total amount of protein metabolism of the body. This is further dependent on the nitrogenous intake. Extensive investigation has been made on the partition of the urinary nitrogen between the urea and ammonia under normal conditions and with different amount of nitrogen in the diet. A large amount, however, of the older work is vitiated by the use of inaccurate methods of analysis. We quote here simply the more recent studies or those in which reliable methods of analysis were employed. Schultze[1] found with a daily excretion of 26 to 36 grams nitrogen, the urea to be 86.3 to 91.6 per cent., and with 17 to 22 grams nitrogen, 83.7 to 88.4 per cent. Gumlich[2] gives the following averages from his investigations:

	Urea N.	NH_3 N.
On mixed diet	85.6 per cent.	4.95 per cent.
On meat diet	87.0 per cent.	4.77 per cent.
On vegetable diet	79.2 per cent.	4.47 per cent.

Camerer[3] found urea N 84 to 87 per cent., and NH_3 N 4.6 to 5.4 per cent. with an excretion of 12 to 17 grams nitrogen, while with excretion of 20 to 22 grams the urea N was increased to 88 to 91 per cent.

Probably the most careful investigation of the partition of urinary nitrogen in health was made by Folin. On a diet according to Voit's standard, a man of average weight excretes daily between 14 to 18 grams of nitrogen in the urine. The partition of the nitrogen between the urea and ammonia is in this case, according to Folin,[4] urea N 86 to 89 per cent., and ammonia N 3.3 to 5 per cent. However, the distribution of the total nitrogen depends on the absolute amount of it present. When protein metabolism is reduced, the ammonia percentage of the total nitrogen rises unless the food is such as to yield an alkaline ash, and the urea suffers a relative as well as absolute decrease. With a reduction of the total nitrogen to 2 to 3 grams, only about 60 per cent. of it is excreted in the form of urea. Haskins[5] confirms Folin's conclu-

[1] Archiv. f. Physiol. (Pflüger's), 1889, xlv, 401.
[2] Zeitschr. f. Physiol. Chem., 1893, xvii, 10.
[3] Zeitschr. f. Biol., 1902, xliii, 13.
[4] Amer. Jour. Physiol., 1905, xiii, 45.
[5] Jour. Biol. Chem., 1906–07, ii, 217.

sions in regard to low protein diet on urea excretion, but finds that the ammonia N is a constant per cent. of the total N. With low protein diet he found the urea N per cent. 71.4 to 82.2. His figures for ammonia N, however, are much higher than those given by other investigators even on a high protein diet. Gammeltoft[1] on a high protein diet with excretion of 10 to 12 grams of urinary nitrogen finds the urea N to be 83.9 to 86.1 per cent., and the ammonia N 3.9 to 4.4 per cent. of the total, while on a low protein diet with an excretion of 5 to 7 grams of urinary nitrogen, the urea N amounts to 76.9 to 81 per cent. and the ammonia N to 5.4 to 6 per cent. of the total.

The limits of normal with varying levels of protein metabolism are therefore rather hard to define sharply. However, one can probably safely conclude that with a urinary nitrogen of 10 grams or more the lower limit for urea N is 80 per cent. and the upper limit for NH_3 N 5 per cent., while with a nitrogen excretion of 5 to 10 grams the lower limit for urea is 70 per cent., and the upper limit for ammonia N is 8 per cent.

Furthermore, excessive acid production in the organism is accompanied with a lowering of the urea percentage and increase in the ammonia percentage of the total nitrogen. An increased elimination of ammonia may, as shown by Munzer in the case of acute phosphorus poisoning, be dependent upon the formation of large quantities of acids, caused by abnormal metabolism, and these acids require a greater amount of ammonia for their neutralization. That an abnormal formation of acid occurs after cutting out the liver has been shown especially by Salaskin and Zaleski.[2]

Although amino acids have been known to occur in urine for a long time, it is only recently that suitable methods for their quantitative estimation have been devised. On account of the comparative newness of the subject, very little data regarding the amino acid content of the urine in health or disease is available. The two methods in general use are the "formol" titration method of Henriques and Sorensen and the nitrous acid method of Van Slyke.

[1] Skand. Arch. of Physiol., 1913, xxviii, 325.
[2] Zeit. f. Physiol. Chem., 1900, xxix, 517.

It is probable that the data given by the two methods are not the same, the "formol" titration method probably giving somewhat higher results. A separation has usually been made of the amino acid content of the urine before and after hydrolysis. The amino acid content before hydrolysis is usually referred to as amino acid N or free amino acid N, while the amino acids obtained after hydrolysis as the total amino N or the difference as the peptid N or conjugated amino N. Levene and Van Slyke[1] found the total amino N to be 1.1 to 2.8 per cent., and the free less than 1.5 per cent. of the total N, while with a more improved method later Van Slyke[2] found the total 1.8 to 3.5 per cent., and the free 0.38 to 0.82 per cent. Using the "formol" titration method the following results have been obtained on normal urines: Henriques[3] gives about 2 per cent. for free amino N and later Henriques and Sorensen[4] give 1 to 2 per cent., while Yoshida[5] found 0.6 to 2.1 per cent. of the total N as free amino N on a mixed diet. Frey[6] found the amino N per cent. of the total independent of changes in the carbohydrate and fat content of the diet, but somewhat higher with a low protein diet than with a high one. Falk and Saxl[7] found that diet exercised no influence on the amino N per cent. of the total nitrogen. Gammeltoft[8] on a high protein diet found amino N to be 1.8 to 2.4 per cent., and on a low protein diet 1.8 to 2.7 per cent. of the total nitrogen.

Using the nitrous acid method, the small number of values for normal urines never exceeded 1.5 per cent. of the total N. We have adopted temporarily 1.5 per cent. as the upper limit of normal for the free amino N of the urine determined by Van Slyke's nitrous acid method. We realize, however, that the normal may later be found to vary within greater limits.

The ingestion of galactose (30 gm.) and levulose (100 gm.), according to Strauss's recent work, does not result in the appearance of the sugar in the urine in health. Any appearance in the urine is due to decreased tolerance for these substances.

[1] Jour. Biol. Chem., 1912, xii, 301.
[2] Ibid., 1913, xvi, 125.
[3] Zeitschr. f. Physiol. Chem., 1909, lx, 1.
[4] Ibid., 1909, lxiii, 27.
[5] Loc. cit.
[6] Zeitschr. f. klin. Med., 1911, lxxii, 300.
[7] Ibid., 1911, lxxiii, 134.
[8] Loc. cit.

The fibrinolytic ferment does not normally occur in human blood serum, and appearance must be taken as an indication of a pathological condition.

The Phenoltetrachlorphthalein Test. Previously the results of eighty applications of the test on sixty-seven patients were reported. The total number of patients studied to date is 113, 33 of whom had no clinical evidence of liver disease. The positive findings in health and in various types of liver disease, together with the appearance of the drug in the urine are shown in Table II.

Table II

	Examined.	Less than 30 per cent.	Urine examined.	Positive.
Cirrhosis	18	9	11	7
Congestion	32	11	10	6
Carcinoma of liver	6	6	3	2
Carcinoma	5	3	3	2
Luetic liver	5	2	2	1
Severe anemia	9	7	1	0
Miscellaneous	5	2	2	2
	80	40	32	20
Normals	33	2	22	3
Total	113	42	54	23

It is evident that a phthalein output of less than 30 per cent. and the appearance of phthalein in the urine is infrequent in health and frequent in anatomically diseased livers. A normal phthalein output does not indicate the absence of a diseased liver, but that demonstrable functional changes do not accompany the anatomical changes. In the eleven cases coming to autopsy, pathological findings contraverting the functional findings have not been encountered. Absence of marked diffuse pathological changes has been found in several instances in which the functional studies showed a good function where clinically severe liver injury was suspected. The autopsy findings served to increase our confidence in this test. In one instance (No. 1 of this series) a microscopic study of the liver suggested greater injury than was shown by the phthalein.

Summary of Findings. Forty-five cases have been studied in this series (see Tables III and IV). The phthalein test was applied in 42 cases with 16 positive findings, while of the 34 cases

in which the presence or absence of this substance in the urine was determined, 21 showed its presence. Fibrinogen was determined in 40 instances, 8 of which were below 350 mg., and 12 below 400 mg., while 8 were above 800 mg., *e. g.*, 20 abnormal findings. The lipolytic activity of the blood was investigated in 39 cases, 5 of which showed an acid production of more than 0.4 c.c. and 3 above 0.5 c.c. The presence of fibrinolytic ferment was tested for in 40 instances, and found in 7, all of which were cirrhoses. The galactose test was applied in 29 and the levulose in 19 cases, the former showing only 4 and the latter 2 positive findings. The total non-protein nitrogen and urea N of the blood were determined in 37 cases. The urea N was less than 40 per cent. of the total in 9 instances. The amino N of the blood was determined in 35 cases, and amounted to more than 3 mg. per 100 c.c. in 25 instances and above 4 mg. in 13 instances. The total N, urea, and ammonia in the urine were determined in 41 cases. The total nitrogen of the urine was above 10 grams in 13 cases, and in these the urea N was below 80 per cent. in 7 instances and the ammonia N above 5 per cent. in 10 instances. Twenty-one cases showed a urinary nitrogen between 5 and 10 gm., and of these 4 cases showed a urea N below 70 per cent., and 11 an ammonia N above 8 per cent. The amino acid content of the urine was investigated in 22 cases, 12 of which showed values above 1.5 per cent. of the total nitrogen.

Liver Cirrhosis. The results in the fourteen cases of cirrhosis studied were as follows: Phthalein studied in feces in 14, positive in 6, in urine in 11, positive in 7; fibrinogen in 14, positive in 6; lipase in 14, positive in 2; fibrinolytic ferment in 14, positive in 7; galactose in 11, positive in 2; levulose in 10, positive in 2; urea N per cent. (blood) in 14, positive in 5; amino N (blood) in 14, positive in 10; urea percentage (urine) in 14, positive in 3; ammonia percentage (urine) in 14, positive in 10; amino N percentage (urine) in 7, positive in 5.

Myocardial Insufficiency. Twelve cases of myocardial insufficiency were studied. Phthalein studied in feces in 9 cases with 1 positive, lowest being 18 per cent., and in urine in 10 cases with 5 positive; fibrinogen in 11 with 1 positive; lipase in 11 cases and positive in 1; fibrinolytic ferment in 12, positive in none;

TABLE III

Number.	Name.	Medical number.	Date.	Clinical diagnosis.	Size cm. below costal margin.	Phthalein per cent. in feces.	Phthalein in urine.	Fibrinogen mgm. per 100 c.c.	Lipase c.c. n/10 acid.	Blood nitrogen partition.				Urinary nitrogen partition.					Galactose.	Levulose.
										T. N. P. N. mgm. per 100 c.c.	Urea N mgm. per 100 c.c.	Urea N per cent. T. N. P. N.	Amino N mgm. per 100 c.c.	Urine c.c. in 24 hours	Total N gms.	Urea N per cent.	Ammonia N per cent.	Amino N per cent.		
1	G. C. T.	31474	Oct. 24, 1913	Atrophic cirrhosis	....	38	....	350 97 (death)	0.25	38	9	24	2.0	700 840	6.4 9.5	65 71	13.0 12.0			
2	J. M.	31703	Nov. 20, 1913	Hypertrophic cirrhosis; carcinoma of liver?	7.5	40	−	467	0.38	37	17	47	2.5	1300	8.5	76	8.9	...	−	−
3	W. K.	31746	Nov. 25, 1913	Atrophic cirrhosis	....	30	....	222	0.28	39	17	44	4.0	....	....	80 76	12.0 10.0	...	−	−
4	J. J.	(Univ. of Md.)	Feb. 10, 1914	Hypertrophic cirrhosis	....	48	....	390	0.20	29	14	47	4.4	350	4.3	59	21.0	3.9	−	−
5	A. G.	32152	Feb. 20, 1914	Hypertrophic cirrhosis; chronic nephritis	8.0	17	+	340	0.53	35	15	43	5.2	1010	5.9	85	3.4	1.7	−	−
6	W. A. S.	32265	Mar. 17, 1914	Cirrhosis; myocardial insufficiency	8.0	23	−	440	0.15	45	22	49	3.7	1800	8.9	81	2.5	1.2	−	+
7	W. F.	32252	Mar. 17, 1914	Cirrhosis; myocardial insufficiency	4.0	18	+	588	0.25	34	16	47	5.4	1430	9.5	88	5.0	1.6	−	−
8	A.	(Bay View)	Mar. 26, 1914	Cirrhosis	....	25	+	1275	0.55	41	17	41	3.9	2220	13.2	86	7.5	2.4	−	−
9	E. G.	31757	Nov. 25, 1913 Apr. 11, 1914	Cirrhosis; myocardial insufficiency	.... 2.0	34 30	−	820 450	0.36 0.28	40 28	12 14	30 50	4.9 3.0	1184 645	6.2 5.6	77 78	10.0 13.0	... ...	− −	− −
10	E. C.	32445	Apr. 21, 1914	Hypertrophic cirrhosis	....	38	++	330	0.30	35	11	31	3.8	1475	4.3	76	7.7	1.7		
11	H.	(Bay View)	Dec. 13, 1913	Atrophic cirrhosis	....	5	+++	120	0.19	29	9	31	2.9	770	4.6	60	15.0			
12	J. D.	32329	Apr. 21, 1914	Cirrhosis of liver? Arterio-sclerosis	Normal	30	−	480	0.14	53	24	47	5.5	1635	16.3	84	8.0	0.8	+	−
13	E. S.	31641	Jan. 6, 1914	Hypertrophic cirrhosis	5.0	44	+	700	0.21	31	9	29	3.8	872 1125	2.5 3.2	81 78	8.2 6.1	...	+	

14	S. H.	31763	Nov. 25, 1913	Hypertrophic cirrhosis; syphilis	8.0	28	+++	306	0.34	25	10	40	3.0	810 775	6.2 5.6	77 78	10.0 13.0	...	−	+
15	W. P.	31578	Nov. 7, 1913	Myocardial insufficiency; syphilis	4.0	37	....	....	0.31	32	18	56								
16	P. H.	31719	Nov. 21, 1913	Myocardial insufficiency	3.5	....	+	390	0.35	35	17	48	4.2	1425	6.3	79	8.0	...	−	−
17	T. P.	31612	Nov. 20, 1913	Myocardial insufficiency	7.0	34	−	630	0.30	35	16	45	...	1070	10.3	78	8.3	...	−	−
18	J. W.	32049	Feb. 20, 1914	Myocardial insufficiency; uremia; chronic nephritis	Normal	48	....	1640	0.42	120	74	62	7.6	2250	12.2	66	2.5	1.4	−	
19	A. V.	32333	Apr. 2, 1914	Myocardial insufficiency; chronic peritonitis	12.0	24	+	520	0.17	36	20	55	3.0	425	1.9	70	4.8	1.2	−	
20	A. McD	31998	Jan. 23, 1914	Myocardial insufficiency	4.0	18	+	530	0.25	33	20	61	6.3	1050	7.9	80	12.6	1.5		
21	M. W.	31988	Jan. 23, 1914	Myocardial insufficiency; diabetes	Normal	....	+	685	0.35	29	11	38	3.2	1570	12.2	79	5.0	1.6		
22	E. T.	31765	Jan. 14, 1914	Myocardial insufficiency	5.0	31	−	829	0.24	37	73	62	5.7	1385	12.2	80	6.9		−	
23	M. B.	31870	Jan. 6, 1914	Myocardial insufficiency	10.0	57	+	267	....	26	11	42	3.2	745	5.9	75	8.5	...	−	
24	C. H.	31904	Jan. 6, 1914	Myocardial insufficiency; uremia; chronic nephritis	Normal	30	−	630	0.28	60	36	60	3.0	310	3.2	78	5.9	1.6		
25	C.	(Bay View)	Jan. 13, 1913	Myocardial insufficiency	5.0	42	−	487	0.38	40	17	43	...	1230	8.9	72	9.3			
26	W.	31774	Dec. 2, 1913	Catarrhal jaundice; cholelithiasis	....	22	+	....	0.50	42	18	43	5.3	1190 1260	11.7 9.1	73 80	6.1 9.0	...	+	−
27	L.	3	Apr. 21, 1914	Myocardial insufficiency	8.0	....	−	360	0.24	39	17	43	3.7	1485	12.3	82	6.6	1.3	−	−
28	C.	(Bay View)	Dec. 13, 1913	Carcinoma with metastases to liver	....	23	−													
29	J. H.	31920	Jan. 6, 1914	Gastric carcinoma, metastases to liver?	....	24	+	536	0.28	34	21	61	3.4	780	7.9	84	7.0	...	−	
30	W. J.	32458	Apr. 21, 1914	Gastric carcinoma	Normal	30	+	....	....	...	..	..	...	620	7.8	76	7.8	1.5		
31	C. H.	31971	Jan. 24, 1914	Splenomyelogenous leukemia	Normal	38	+	....	....	...	..	..	...	1175	7.3	79	3.7	1.6	−	?

TABLE III—(Continued)

Number.	Name.	Medical number.	Date.	Clinical diagnosis.	Size cm. below costal margin.	Phthalein per cent. in feces.	Phthalein in urine.	Fibrinogen mgm. per 100 c.c.	Lipase c.c. n/10 acid.	Blood nitrogen partition.				Urinary nitrogen partition.					Galactose.	Levulose.
										T. N. P. N. mgm. per 100 c.c.	Urea N mgm. per 100 c.c.	Urea N per cent. T. N. P. N.	Amino N mgm. per 100 c.c.	Urine c.c. in 24 hours.	Total N. gms.	Urea N per cent.	Ammonia N per cent.	Amino N per cent.		
32	C. R.	31565	Oct. 25, 1913	Splenomyelogenous leukemia	Normal	43	....	510	0.19	...	..	..	...	700	9.2	83	4.9	1.0		
			Jan. 6, 1914			46	−	250	0.28	33	14	42	6.2	1390	12.1	82	4.4	0.8	−	−
33	C.	.....	Oct. 24, 1913	Uncinariasis with anemia	....	23	....	456	0.21	...	..	..	...	1240	10.5	78	8.4			
34	E. W.	31704	Jan. 14, 1914	Pernicious anemia	Normal	27	....	....	....	...	..	..	...	1480	6.3	64	14.0			
35	J. F.	32312	Mar. 26, 1914	Pernicious anemia	Normal	23	−	....	....	...	..	..	...	1530	8.7	76	13.1	1.0	−	−
36	M. H.	32436	Apr. 21, 1914	Syphilitic hepatitis	5.0	24	+	822	0.21	33	8	24	2.7	520	2.8	63	17.0	2.5	−	
37	H.	(Bay View)	Mar. 26, 1914	Syphilitic hepatitis	....	32	−	780	0.07	40	17	42	3.9	1790	4.3	69	8.4	7.5	+	
38	C. C.	31900	Jan. 6, 1914	Polyserositis; tuberculous syphilis	6.0	30	+	627	0.19	29	9	31	3.2	815	6.2	70	15.0	2.3	−	
39	J. D.	31742	Nov. 25, 1913	Polyserositis, tuberculous	6.0	31	+	887		...	..	..	...	880	8.9	76	10.0	...		
								672	0.36	30	11	36	2.7	830	6.5	77	8.0	...	−	−
40	A. W.	32139	Feb. 20, 1914	Congenital hemolytic jaundice	6.0	31	....	354	0.25	32	16	50	3.7	2230	15.6	79	5.4	1.6	−	−
41	J. T.	32443	Apr. 23, 1914	Acute lobar pneumonia; jaundice	Normal	24	+	716	0.20	41	22	53	2.5	2580	17.0	80	8.1	0.6		
42	R.	(Obstetric)	Feb. 20, 1914	Nephritis in pregnancy; eclampsia	.....	47	....	584	0.25	33	16	48	4.1	1610	8.5	80	5.0			
43	R. A.	32355	Apr. 18, 1914	Salvarsan poisoning	....	....	....	....	1.00	150	..	..	12.4							
44	M. S.	31496	Oct. 24, 1914	Pentosuria; peripheral neuritis	....	....	....	....	....	...	..	..	...	1050	11.9	76	5.7			
					....	39	....	....	0.29	...	..	..	...	850	13.0	79	5.0			
45	J. S.	(Surgical) 33712	Jan. 24, 1914	Gallstones; operation draining	Normal	4	++	830	0.27	33	15	45	2.8							

The following cases showed the presence of fibrinolytic ferment in the blood: Nos. 1, 3, 5, 7, 11, and 14.

galactose in 7, positive in none; levulose in 3, positive in none; urea N per cent. (blood) in 12, positive in 1, in which 6 were over 50 per cent., and 3 over 60 per cent.; amino N (blood) in 9, positive in 7.

The functional injury in liver cirrhosis is relatively greater than in chronic passive congestion, for a consideration of all the tests in each condition indicates that in 10 of the 14 cases of cirrhosis there was definite functional injury, 3 with less marked injury and only one with a practically normal function throughout, while in chronic passive congestion only 4 showed definite decrease, while 7 showed a practically normal function.

Carcinoma of Liver. Little data outside of the phthalein has been collected. C. 28, who definitely had metastasis to the liver, showed a 23 per cent. output five months before death. H. 29, with gastric carcinoma and clinically thought to have metastasis to the liver, showed a 24 per cent. phthalein positive in urine and the urea only 21 per cent of the T. N. P. N. of blood. These cases are in keeping with the 3 cases of liver carcinoma reported last year in which the phthalein excretion was 8, 14 and 7 per cent. respectively. However, slight decrease in phthalein, *e. g.*, 20 to 25 per cent. does not indicate liver carcinoma, since such findings have been found in gastric carcinoma when no proof of liver metastasis was at hand, in which case it is merely the expression of the influence of anemia and cachexia on liver function.

Anemia. Experimentally and clinically a severe grade of anemia depresses the function of the liver as indicated by phthalein. That there is also a decrease in the fibrinogen has been shown by Whipple, but owing to the quantity of blood necessary for carrying out the test, it is not applicable in all cases of anemia. Changes in the urinary N partition may appear.

Luetic Hepatitis. Of the two cases studied one showed normal phthalein, a low lipase, urinary nitrogen partition changes and a positive galactose, while the other showed a low phthalein content in feces, positive in urine, an abnormally high fibrinogen, low urea per cent. of T. N. P. N. in blood, and urinary nitrogen partition changes.

Polyserositis. Two cases with much the same clinical condition and both with large livers showed practically identical findings, *e. g.*, normal phthalein in feces but positive in urine, fibrinogen and lipase normal, low urea per cent. of T. N. P. N. in blood, changes in urinary N partition but no decreased tolerance for sugar.

Table IV

	Total number of tests.	Total number of positive tests.	Cirrhosis of liver.		Myocardial insufficiency		Carcinoma.		Syphilitic hepatitis.		Pernicious anemia.		Polyserositis.		Miscellaneous.	
No. of cases tested.			14		12		3		2		2		2		10	
Name of test				+		+		+		+		+		+		+
Phthalein in feces	42	16	*14*	6	*9*	1	*3*	2	*2*	1	*2*	2	*2*	0	*9*	4
Phthalein in urine	34	21	*11*	7	*10*	5	*3*	2	*2*	1	*1*	0	*2*	2	*5*	4
Fibrinogen	36	8	*14*	6	*11*	1	*1*	0	*2*	0	—	—	*2*	0	*1*	1
Fibrinolytic ferment	40	7	*14*	7	*12*	0	*1*	0	*2*	0	—	—	*2*	0	*9*	0
Lipase	39	5	*14*	2	*11*	1	*1*	0	*2*	0	—	—	*2*	0	*9*	2
Galactose	29	4	*11*	2	*7*	0	*1*	0	*2*	1	*1*	0	*2*	0	*4*	2
Levulose	18	2	*10*	2	*3*	0	*0*	0	—	—	*1*	0	*1*	0	*3*	0
Blood—																
Urea N %	37	9	*14*	5	*12*	1	*1*	0	*2*	1	—	—	*2*	2	*6*	0
NH_2N	35	25	*14*	10	*9*	7	*1*	1	*2*	1	—	—	*2*	1	*6*	4
Urine—																
Urea N %	41	11	*14*	3	*11*	3	*2*	0	*2*	2	*2*	1	*2*	0	*8*	2
NH_3N %	41	28	*14*	10	*11*	7	*2*	0	*2*	2	*2*	2	*2*	2	*8*	5
NH_2N %	22	12	*7*	5	*6*	2	*1*	0	*1*	2	*1*	0	*1*	1	*5*	2

Explanation: The figures in italics represent the number of times tests were made and the other figures indicate the number of positive results in the various types of diseases.

Necessity for Combined Renal and Liver Functional Studies. In view of the facts that nitrogenous metabolism and the permeability of the kidney to sugars are markedly affected by renal diseases, a careful investigation of the functional capacity of the kidney should be made in all cases in which sugar tolerance, urea or blood nitrogen partition are entering into consideration, as in phosphorus and $CHCl_3$ poisoning in dogs or in myocardial insufficiency or anemia. Renal injury is suggested in cases 15, 33, and 43. The relative effect on liver and kidney function of general conditions such as anemia and myocardial insufficiency are worthy of investigation. A report of such a study will appear later in collaboration with Dr. R. R. Snowden.

Acidosis and Liver Function. It would have been advisable to have attempted to exclude increased ammonia excretion in the urine, by feeding alkalies (sodium bicarbonate, sodium citrate), since the NH_3 increase may be merely the expression of an acidosis.[1 2 3 4] This, unfortunately, has not been done but is contemplated in future studies.

Practicability of Tests. *The phthalein test* involves an intravenous injection and careful collection of stools for forty-eight hours. Not more than ten minutes are required for carrying out the determination of the phthalein after the feces are removed from the shaker. Three undesirable features are connected with its application: (1) The quality of red color obtained in certain instances (10 to 20 per cent. of the cases) is such that accurate quantitative estimation is difficult. Only in rare instances is this a serious difficulty leading to error of more than 5 per cent. (2) Thrombosis frequently follows at the point of injection, as evidenced by slight local pain or tenderness together with resistance offered to the palpating finger along the course of the vein. This occurred in eight instances in this series of cases, but in no case has it occasioned serious discomfort or resulted in actual harm to the patient. (3) With salt solution made with freshly distilled water chills following the injection are infrequent. When no dilution is employed chills are less frequent and not accompanied with increase in temperature.

Fibrinogen determination is inapplicable in the presence of severe anemia. It necessitates the withdrawal of 40 to 50 c.c. of blood. A high-speed centrifuge and considerable chemical equipment are requisites. The test is time-consuming.

Lipase determination is readily applied, requiring neither complicated apparatus nor expenditure of much time.

The determination of the total non-proteid nitrogen, urea N and amino acid N of the blood can not be carried out when severe anemia exists. Technically the determinations are easy but they are time-consuming.

[1] Camerer, Zeitschr. f. Biol., 1902, xliii, 13.
[2] Haskins, Jour. Biol. Chem., 1906–7, ii, 217.
[3] Janney, Zeitschr. f. Physiol. Chem., 1911–12, lxxvi, 99.
[4] Sellards, Johns Hopkins Hosp. Bull., 1912, xxiii, 289.

The nitrogen partition in the urine requires somewhat less time. Galactose can be administered without discomfort to the patient, but technical difficulties attend the use of levulose, at least 25 per cent. of the patients refusing to take the full amount or developing nausea or vomiting following its ingestion. Its findings are therefore vitiated.

The fibrinolytic ferment is readily determined if present.

Urobilinogen determinations in the urine are valueless unless made daily for a period of two weeks and unless associated with urobilin determinations in the feces.

CONCLUSIONS. 1. Outspoken changes in liver function can be demonstrated in most cases of advanced liver cirrhosis, in markedly congested livers associated with myocardial insufficiency, in carcinoma of liver, in luetic livers, and in conditions of cachexia with marked anemia.

2. Functional changes have been most marked in cirrhosis, in neoplasm of liver and in cachetic conditions with severe grades of anemia. The functional changes in chronic passive congestion have not been frequent or pronounced.

3. Harmony in the findings of the tests is present in some cases, *i. e.*, most of the tests indicating a decreased function or indicating a normal function, but in other instances the function in an individual case appears normal by some tests and diminished by others and absolutely no parallelism exists between the findings of the various tests in the latter instance, *i. e.*, with one test indicating decrease in function it is impossible to predict what the other tests will show.

4. From this small series of cases it is impossible to reach definite conclusions concerning the absolute and relative value and limitations of these various tests, but the following impressions are the outcome of our limited experience:

(*a*) Under clinical conditions a phthalein output under 30 per cent. or the appearance of phthalein in the urine is of unquestionable significance. When in accord, *i. e.*, both positive or both negative, the evidence is of more value than single or discordant findings. Positive value is not claimed for negative findings. A marked decrease in phthalein means a decided injury to liver

function. Autopsies in 11 cases have increased our belief in the value of this test.

(*b*) Low fibrinogen values are frequently but inconstantly encountered in cirrhosis which confirms the results reported by Whipple. Marked positive findings may carry prognostic significance, although they may not appear until shortly before death. Negative findings have no value.

(*c*) The determination of the lipolytic activity of the blood plasma furnishes very little or no information of prognostic or diagnostic significance in these types of clinical cases. Only in two or three instances have the clinical findings been comparable with our findings or those of Whipple in $CHCl_3$ or phosphorus poisoning. High values probably carry prognostic significance.

(*d*) Dr. Goodpasture's fibrinolytic ferment studies on this series of cases show that this ferment is present only in cirrhosis and hence when present of definite diagnostic importance.

(*e*) Bauer's galactose test is applicable without discomfort to the patient, but yields no information of consequence.

(*f*) Strauss's levulose test was attended with technical difficulties—nausea and vomiting frequently following its employment, and yielded information of no consequence in the limited number of cases in which it was successfully carried out.

(*g*) Blood N partition: Cumulative phenomena have not been encountered in this series except with coexistent renal disease.

The urea N percentage of total has been 40 per cent. or less in several instances, and especially low in cases of advanced cirrhosis.

The NH_2N has been high in a considerable proportion of the clinical cases. (In phosphorus poisoning the NH_2N increase was always present and was associated with increase in the urea N and total non-proteid nitrogen. In chloroform poisoning the absolute and relative values of the various forms of nitrogen did not vary from normal.)[1]

(*h*) Urinary Nitrogen partition: No instance of absolute normal urinary nitrogen partition has been encountered. However, the low level of protein metabolism so often present, together with

[1] Studies on Liver Function in Phosphorus and Chloroform Poisoning. To be published shortly.

the non-exclusion of acidosis, render the interpretation of the N distribution somewhat difficult. Practically all the cirrhosis cases showed definite N partition changes.

The NH_3N and NH_2N were definitely increased in most of the cases studied and particularly in cirrhosis.

Concerning the relative merits of these tests it appears that the phthalein, the fibrinogen, the blood and urine nitrogen partitions are of decided value in determining the presence and to a less degree the extent of functional involvement, while the demonstration of the presence of a fibrinolytic ferment is of decided diagnostic importance. The determination of sugar tolerance and of the lipolytic activity of the blood apparently afford information of much less value.

In this study marked variations from the normal have been indicated in many patients. Opportunity for studying only a limited number of types of liver injury has been afforded. The application of such studies to eclampsia, acute yellow atrophy, liver abscess, obstructive jaundice, etc., is most desirable, and also, to miscellaneous types of disease, in order to determine if the changes described above are specific to liver disease.

The information derived from these liver studies does not compare in diagnostic and prognostic importance with that from corresponding renal functional studies. This may depend upon several factors, the limited number of cases of severe liver injury under observation, the possible existence of a great "factor of safety" in the liver whereby in case of necessity function is carried on efficiently by a relatively small proportion of liver substance, the prognosis in many of these cases being controlled by factors other than decreased liver function, *e. g.*, myocardial insufficiency, carcinoma, lues, anemia, etc., and the lack at present of correlation of anatomical, clinical and functional findings occasioned by the newness of the subject. The results, however, encourage us in the belief that scientifically and also clinically this subject is worthy of extensive investigation.

APPENDIX[1]

No. 1, Med. No. 3147. G. C. T., aged forty-seven years, male, white, September 19, 1913.

Clinical Diagnosis. Cirrhosis of liver, pulmonary tuberculosis, tuberculosis of larnyx, ascites, bronchopneumonia. Pains in abdomen, swelling of abdomen and legs; duration four months. Markedly alcoholic. Hemoptysis and hemorrhoids. On admission weakness, emaciation, ascites, dilated veins on abdomen, liver dulness from sixth rib to 8 cm. below costal margin. Edema of extremities. Jaundice. Hemoglobin, 62 per cent. Wassermann negative. Repeated abdominal tappings. Injected October 23. Died November 19. *Autopsy:* No. 4024. (Dr. Whipple.) Anatomical diagnosis: Diffuse cirrhosis of liver (atrophic type); chronic pancreatitis; passive congestion of abdominal viscera; chronic fibroid apical tuberculosis; chronic laryngeal tuberculosis; general anasarca; emaciation; bronchopneumonia (organizing); congestion and edema of lungs; acute aortic endocarditis; acute splenic tumor; chronic gastritis; chronic ulcerative laryngitis (tuberculous). Microscope: A pretty diffuse type of cirrhosis. New formed connective tissue contains a good many new formed bile ducts, and mononuclear wandering cells. There is increase in connective tissue in many of the small lobules of hepatic parenchyma. The liver epithelium looks much damaged although some of the cells show a good deal of hypertrophy. Others show much pigmentation and various types of degeneration, even necrosis. Bile canaliculi in some liver cells are conspicuous. There is very little liver parenchyma which seems even approximately normal. Liver weighs 1480 gms. It presents the typical picture of Lænnec cirrhosis. The capsule is thickened and rather milky. The surface is coarsely granular, showing areas sticking above it. Collateral circulation in the suspensory ligament is very conspicuous. The gall-bladder is dilated, thin walled, but the bile passages are normal. On section parts of the organ show very extensive scarring, whereas other portions show a more diffuse and not so extensive involvement. There are nodules and lumps of liver parenchyma of all sizes between the scars. These nodules may be gray or pigmented yellowish-brown. There are bright red areas apparently associated with hemorrhage and perhaps necrosis in some of the liver cells. The architecture is greatly obliterated. The left lobe is thin, flattened and elongated, but in general presents the same changes found in the right lobe. The organ is very firm and hard. Mucosa of gall-bladder normal.

No. 2, Med. No. 31703. J. W. M., aged fifty-four years, male, white, November 20, 1913.

[1] We are indebted to Professor G. H. Whipple for the careful pathological study of sections from the cases coming to autopsy.

Clinical Diagnosis. Cirrhosis of liver. Carcinoma of liver (?). Alcoholic. Swelling of abdomen for six weeks, diarrhea for three weeks; loss of weight. No myocardial insufficiency. Ascites, liver dulness from fourth is to 7.5 cm. below costal margin; liver surface irregular and granular, suggesting neoplasm to some observers. Red blood cells, 2,780,000; white blood cells, 10,400; hemoglobin, 53 per cent. Tapping on two occasions, liver easily palpable, "finely nodular." Predominating opinion was that patient had cirrhosis, but the possibility of neoplasm was considered.

No. 3, Med. No. 31746. W. J. K., male, aged forty years, November 25, 1913.

Clinical Diagnosis. Cirrhosis of liver. Hydrothorax. Markedly alcoholic (bartender by occupation) for years. Bleeding hemorrhoids for seven years, swelling of ankles for one and a half years, later swelling of abdomen; hematemesis and bloody stools on two occasions. On admission: anemia, red cells, 2,920,000; hemoglobin, 55 per cent.; white blood cells, 2925; slight jaundice, ascites, enlarged superficial veins on abdomen; liver flatness from fourth rib to within 2 cm. of costal margin; moderate edema of ankles. After removal of 8 liters of fluid from the abdominal cavity liver dulness extended to costal margin, edge was not felt. Wassermann positive. Rapidly recurring ascites, necessitating tapping as often as once a week. Urine negative for albumin and casts except on day of admission. Death five months after tests were made. *Autopsy:* No. 4132, May 21. Atrophic cirrhosis of liver; portal stasis, ascites, dilated collateral circulation; organizing thrombosis of portal vein and its radicles; chronic interstitial hyperplasia of spleen; chronic interlobular pancreatitis; pancreatic necroses; hemorrhages into islands of Langerhans; chronic interstitial nephritis, jaundice, chronic fibrous pleuritis, bilateral atelectasis (lower lobes), chronic local peritonitis, perihepatitis and splenitis. Liver: Very small. Surface is nodular, weight 810 gms. Nodules of greenish yellow parenchyma measuring 4 to 5 mm. between which are dense connective-tissue bands. Branches of the portal vein show organized thrombi, some of which are completely occluding. Microscope: Cirrhosis is of annular type. Some of the scars are very dense and extensive. Proliferation of bile ducts not conspicuous. New formed connective tissue rich in wandering cells. Islands of liver tissue in places well preserved, showing hypertrophy of liver epithelium. In other places there are focal necroses and areas of fatty degeneration. Many of the liver cells contain yellow, granular pigment. The bile canaliculi are conspicuous, and distended with greenish, colloid material. Organizing thrombi present in portal vessels. One might estimate roughly that one-third to one-half of the remaining liver parenchyma shows definite degeneration, which should interfere with functional activity.

No. 5, Med. No. 32152. A. G., aged forty-five years, male, white, February 20, 1914.

Clinical Diagnosis. Cirrhosis of liver. Chronic nephritis. Psoriasis. Chronic bronchitis. Indefinite history of stomach trouble, loss of appetite and occasional attacks of belching, nausea and vomiting, extending over a period of twelve years. Previous admission to hospital, July, 1906, at which time a diagnosis of cirrhosis of the liver was made; liver extended 8 cm. below costal margin in right mammillary line. On present admission liver dulness extended three fingers' breadths below costal margin in mammillary line, slight dilatation of superficial veins on abdomen and psoriasis. Liver edge was firm, smooth, fairly sharp, surface smooth. Wassermann negative.

No. 6, Med. No. 32265. W. A. S., aged forty-six years, male, white, March 17, 1914.

Clinical Diagnosis. Cirrhosis of liver, myocardial insufficiency, aortic insufficiency (?), chronic nephritis (?). For about a year patient had dyspnea, orthopnea, tightness in the chest. Three months before admission the abdomen and legs began to swell. Blood-pressure has been elevated. On admission, pigmentation of exposed parts, icteric tint to scleræ, evidences of fluid in right pleural cavity, cardiac dulness 14.5 cm. to left and 5 cm. to right, snapping first sound at apex preceded by a short rumbling murmur, and followed by a soft blow, transmitted to posterior portion of axilla, ascites, enlarged liver, extending 10 cm. below tip of ensiform with rounded firm edge. Spleen not felt, edema of extremities present. Wassermann negative. Paracentesis March 27, 6500 c.c., dark, straw-colored fluid obtained, which showed some red cells in centrifuged specimens. After removal of the fluid the liver was felt plainly and a firm, hard rounded edge was made out about 8 cm. below costal margin in parasternal line and 12 cm. below the ensiform. On discharge, April 23, liver was thought by Dr. Thayer to be softer than on admission: the border was felt three fingers' breadths below the costal margin and 8 cm. below the xiphoid; surface was smooth. Urine showed albumin 2 to 5 gms. per liter and casts constantly. Blood-pressure 130 to 145.

No. 7, Med. No. 32252. W. F., aged fifty-one years, male, white, March 17, 1914.

Clinical Diagnosis. Tuberculosis (eye test). Pleurisy with effusion, thickened pleura. Myocardial insufficiency. Enlarged liver. Cirrhosis of liver (?). For five months shortness of breath on exertion and swelling of abdomen. Not markedly alcoholic. On admission slight yellowish tinge to scleræ, fluid in left pleural cavity, edema of both bases, cardiac dulness 12.5 cm. to left in fifth interspace, 5 cm. to right in fourth interspace, liver enlarged (three fingers' breadths below costal margin in right nipple line), moderate edema of the feet and ankles. Wassermann negative. Tuberculin test (Calmette) 1 per cent. positive. Under rest in bed all signs of myocardial insufficiency disappeared and patient was discharged. Liver at time of discharge seemed to be same size as on admission. Urine showed trace of albumin from time to time; no casts. Blood-pressure normal.

No. 9, Med. No. 31757. E. G., aged forty-three years, male, November 25, 1913.

Clinical Diagnosis. Chronic nephritis, myocardial insufficiency, dilated aortic arch, syphilis (Wassermann). Two previous admissions to hospital at which time same diagnosis was made. Trouble began in October, 1912, one year before admission, with dyspnea, orthopnea and edema of the face, ankles, and legs. Recovered after prolonged rest in the hospital on two separate occasions. Recurrence of symptoms two weeks before admission. On admission patient showed orthopnea, general anasarca, edema of both lungs, wide area of cardiac dulness (15 cm. to left and 5 cm. to right), ascites. After removal of 7.5 liters of fluid liver edge was palpable about 2 cm. below costal margin in the right mammillary line, not palpable in the median line. Liver border was firm. Wassermann positive. Urine showed albumin 1 to 2 gm. to liter and casts constantly; blood-pressure 160 to 210. Pulse persistently rapid. The interesting feature in this patient was the small size of liver in spite of the evidence of a marked chronic passive congestion.

No. 10, Med. No. 32445. Mrs. E. C. C., aged thirty-four years, female, white, April 21, 1914.

Clinical Diagnosis. Cirrhosis of liver. Patient accidentally noticed 15 months ago that she could feel her liver, and since that time the liver has gradually grown larger and firmer. She has always been constipated. Eleven months ago amebæ were said to have been found in the stools, which contained blood and mucus at the time. Emetine treatment cleared up the trouble. Hemorrhoids five weeks ago. On admission (Dr. Thayer) no jaundice, heart not remarkable, dilatation of veins over thorax and abdomen with current running upward. Border of liver was felt, edge sharp and firm on right, a little rounded on left, surface smooth and liver certainly harder than normal. Free fluid in abdominal cavity. Wassermann negative. Urine negative.

No. 12, Med. No. 32329. J. D., aged seventy-one years, male, white, April 21, 1914.

Clinical Diagnosis. Arteriosclerosis, myocardial insufficiency. Pulsus irregularis perpetuus. Chronic nephritis. Emphysema. Cirrhosis of liver. For six months before admission patient had swelling of legs, shortness of breath, and soreness in abdomen. Has been a heavy drinker for forty years. On admission he showed enlarged heart (12 cm. to left and 3 cm. to right by percussion), irregular pulse, liver dulness 3 cm. above costal margin, ascites and edema, with marked arteriosclerosis. Wassermann negative. Urine showed trace of albumin and a few casts. Blood-pressure, 200 on admission, fell to 130 to 140 after rest in bed. This case is evidently not one of outspoken cirrhosis of the liver as the diagnosis seems to rest on the presence of marked alcoholic history and a small liver although a moderate grade of myocardial insufficiency with chronic passive congestion was present.

No. 13, Med. No. 31641. E. S., aged fifty-four years, female, white, October 29, 1913.

Clinical Diagnosis. Cirrhosis of liver. Alcoholic, whisky every day for ten years. Swelling of legs and abdomen and tenderness at right costal margin, duration four weeks. No myocardial insufficiency; ascites, dilatation of superficial veins on abdomen. Wassermann negative. After tapping liver edge was palpable three fingers' breadths below costal margin, sharp, hard, and coarse nodules were palpable on the surface. Repeated tappings performed, hemorrhagic fluid being obtained on several occasions. Under potassium iodide patient improved; ascites finally disappeared and on last examination liver was palpable two fingers' breadths below costal margin, and no nodules were felt. Urine negative. Patient was injected December 7, while there were ascites.

No. 14, Med. No. 31763. S. H., aged fifty-one years, white, male, November 28, 1913.

Clinical Diagnosis. Cirrhosis of liver, syphilis (Wassermann). Pain in abdomen, weakness, loss of weight and swelling of abdomen; duration three months. Not alcoholic. On admission slight jaundice, general glandular enlargement, ascites. Urine showed a trace of albumin occasionally, no casts. After removal of 5.5 liters of fluid from abdominal cavity liver edge could not be definitely felt, but there was dulness several cm. below costal margin in mammillary line. Spleen was enlarged and firm. Wassermann positive. Red blood cells, 3,608,000; hemoglobin, 77 per cent.; white blood cells, 6680. The ascites recurred rapidly and patient had to be tapped repeatedly. At times there was a slight elevation of temperature but for the most part temperature remained normal. He did not improve under antiluetic treatment.

No. 15, Med. No. 31578. W. P., aged thirty-eight years, male, colored, November 7, 1913.

Clinical Diagnosis. Syphilis (Wassermann). Arteriosclerosis. Chronic nephritis. Mitral and myocardial insufficiency. For a year previous to admission patient had dyspnea following a "cold." For two weeks before admission abdomen began to swell. On admission patient showed signs of a marked myocardial insufficiency: dyspnea, orthopnea, edema of lungs with hydrothorax on the right side, enlarged heart (15 cm. to left and 5.5 cm. to right of mid line), systolic murmur at the apex, tachycardia, liver dulness 4 cm. below right costal margin, ascites, edema of genitalia and extremities, as well as walls of heart and abdomen. Blood-pressure 180 to 200. Urine showed albumin and casts constantly. Phenolsulphonephthalein output: First hour, 9 per cent.; second hour, 7 per cent.; total, two hours, 16 per cent. Wassermann positive. Despite rest in bed and use of heart stimulants, compensation was never restored and patient died February 4, 1914. *Autopsy:* 4064. Anatomical diagnosis: syphilitic aortitis involving the aortic valves and secondary chronic aortic

endocarditis; cardiac hypertrophy and dilatation (left); pulmonary thrombosis (right pulmonary artery) associated with fibrosis, induration and bronchiectasis of lower right lobe; chronic passive congestion of lungs; right-sided cardic hypertrophy and dilatation; chronic passive congestion of viscera; edema; ascites; pericardial effusion; chronic fibrous pleurisy (bilateral); chronic perihepatitis. Liver weighs 1150 gm., measures 24 x 15 x 6 cm. It shows a definite thickening of the capsule over the right lobe particularly in the region of the gall-bladder which, however, only extends through the capsule. Elsewhere the Glissonian capsule is delicate and translucent. On section the lobulation is distinct and somewhat irregular. In some zones the lobules are small and atrophic with depressed reddish black centres, while in other areas the lobules are larger and the liver tissue of a more homogeneous yellowish color with the centres less definitely congested. Liver shows a picture of long standing chronic passive congestion with lakes of blood in the region of the central vein and some slight increase in connective tissue in this area.

No. 16, Med. No. 31719. R. H., aged forty-one years, male, black, November 21, 1913.

Clinical Diagnosis. Syphilis (Wassermann), aortic insufficiency, myocardial insufficiency, dilated aortic arch, chronic nephritis, tabes dorsalis. Shortness of breath, cough, and swelling of legs for one week. On admission sluggish pupils, general anasarca, enlarged heart, edema of lungs, liver dulness 3.5 cm. below costal margin in mammillary line; ascites. Wassermann positive in blood and spinal fluid. Pleocytosis and increased globulin in cerebrospinal fluid. Under treatment signs of myocardial insufficiency disappeared, liver dulness was two fingers' breadths below costal margin on discharge.

No. 17, Med. No. 31612. T. P., aged forty-five years, male, November 20, 1913.

Clinical Diagnosis. Ateriosclerosis. Aortic insufficiency, myocardial insufficiency, dilated aortic arch, chronic nephritis; dyspnea and edema for eighteen months previous to this admission, which was the fifth. Markedly alcoholic. On admission he showed evidence of broken compensation, dyspnea, orthopnea, hydrothorax, wide area of cardiac dulness (17.5 cm. to left and 5.5 cm. to right), systolic murmur at apex, diastolic at the base, irregular pulse, ascites and edema. Liver was enlarged on admission, 13 cm. below costal margin in right mid line and 8 cm.below xiphoid. At time of injection cardiac dulness was 17 cm. to left and 6 cm. to right and liver dulness extended 7 cm. below the costal margin in the right mammillary line. The liver was still somewhat tender. Patient had evidently an extensive chronic passive congestion of the liver. Urine always showed albumin and casts and the blood-pressure was always elevated. Patient had two subsequent admissions and died in the hospital; no autopsy.

No. 18, Med. No. 32049. J. H. W., aged forty-five years, male, black, February 20, 1914.

Clinical Diagnosis. Syphilis (Wassermann), chronic nephritis, uremia, myocardial insufficiency, aortic insufficiency, dilated aortic arch, parotitis. For five days previous to admission patient had epigastric pain, shortness of breath, and swelling of abdomen. On admission he showed evidences of myocardial insufficiency, not marked, however, aortic insufficiency, enlarged heart, liver dulness one finger's breadth below costal margin, moderate edema of the extremities. Blood-pressure, 170 to 210. Urine showed constantly albumin and casts. Patient became very drowsy and developed a terminal parotitis. Died March 13. *Autopsy:* No. 4089. March 13, 1914. Subacute nephritis, hypertrophy of left ventricle; syphilitic aortitis; parotitis; pulmonary congestion; bronchopneumonia; cloudy swelling of viscera; rather old tuberculous lymphadenitis (bronchial lymph gland); lymphatic hyperplasia; mesenteric lymphadenitis. Microscope: Liver shows a moderate grade of cloudy swelling. Some of the liver cells contain an excess of granular golden yellow pigment. Others contain a few small fat droplets. Otherwise normal. Liver measures 27 x 19 x 8 cm.; weighs 1900 gm. The surface is smooth and glistening. The capsule is everywhere thin. On section the organ has a brown color. The lobulation is markedly prominent and regular. In localized areas there are scattered reddish dots suggesting dilated bloodvessels. The organ has a slightly boiled appearance.

No. 19, Med. No. 32333. A. V., aged thirty-one years, female, black, April 2, 1914.

Clinical Diagnosis. Syphilis (Wassermann). Mitral stenosis and insufficiency, tricuspid and myocardial insufficiency, chronic peritonitis, hydrothorax, dilated aortic arch. For four years has had shortness of breath, swelling of ankles, and swelling of abdomen. Two previous admissions to hospital, during each of which it was thought that she had cirrhosis of the liver in addition to the myocardial insufficiency; had many tappings, after which she felt fairly well until five months when symptoms recurred. On admission she showed signs of marked myocardial insufficiency; orthopnea, dyspnea, edema of the lungs, tachycardia, heart enlarged to the left, ascites, edema of the extremities. After tapping liver was palpable as a firm, irregular, nodular, tender, pulsating mass extending 12 cm. below costal margin in right mammillary line. Wassermann positive. Repeated tapping of peritoneal cavity necessary. Died April 15. *Autopsy:* No. 4108. April 16, mitral stenosis and insufficiency, chronic valvular endocarditis, pulmonary congestion; pulmonary and tricuspid insufficiency; cardiac hypertrophy and dilatation, especially of right side; chronic passive congestion of lungs and viscera, acute and chronic adhesive peritonitis, acute and chronic perihepatitis; atrophy and fibrosis of liver with areas of hypertrophy; chronic peri and interstitial splenitis;

acute and chronic endometritis; actute salpingitis; acute and chronic adhesive pleurisy (right), bilateral pleuritic effusion, atelectasis, mural thrombus, soldier's patches, subepicardial hemorrhages, pericardial effusion; tuberculous hilic lymph glands; acute and chronic lymphadenitis; syphilitic aortitis, edema of extremities; decubitus ulcer; hemorrhoids, pyorrhea alveolaris. Liver weighs 1800 gm. with the spleen attached, measures 26 x 15 x 7 cm. It is slightly larger than normal. The spleen is attached to the lower margin of the left lobe of the liver by rather dense adhesions and a portion of this lobe is pulled down forming a round bridge between the liver and the spleen. This pulled-out lobe is about 5 cm. from the edge of the liver. The diaphragm is firmly adherent to the spleen by the large, firm, cord-like adhesions which have a red, inflamed surface. In between these adhesions there is a serofibrinous exudate. The capsule of the spleen is markedly thickened. The liver surface is covered by dense adhesions binding it to the diaphragm and abdominal wall. The diaphragm is bound to the liver by cord-like adhesions about $\frac{1}{2}$ to 1 inch in length, and form numerous compartments between the liver and diaphragm. These compartments are filled with large amounts of serofibrinous exudate. There is an acute hemorrhagic appearance to the surface of the liver and about all these adhesions. On section the liver cuts with considerable resistance. The capsule is definitely thickened, measuring about 3 mm. and is of a grayish fibrous appearance. The surface of the liver presents a varied appearance. In general it has a greenish slightly bile-stained appearance. There are numerous areas of atrophy and scar formation. In other places there is a great increase of interstitial tissue with large liver lobules being scattered throughout. There is no evidence of marked contraction or cirrhosis, but the portal areas are distinctly contrasted with the markedly injected central area about which is evident atrophy of the liver substance. The picture is that of a chronic passive congestion with marked atrophy and area of hypertrophy, with great increase in interstitial connective tissue with small areas of scar formation. Microscope: Chronic passive congestion with extreme atrophy. In places liver cells show hypertrophy. There is an increase in connective tissue and in some areas there is a definite fibrosis with proliferating bile ducts. Nothing that could be called a true cirrhosis is found. Section has a thick fibrous capsule. Considerable pigmentation is present.

No. 20, Med. No. 31998. A. McD., aged fifty-nine years, male, black, January 23, 1914.

Clinical Diagnosis. Arteriosclerosis, myocardial insufficiency, pulsus irregularis perpetuus, bronchopneumonia. Several periods of shortness of breath and swelling of ankles. Duration of present attack ten days. On admission signs of marked myocardial insufficiency; dyspnea, orthopnea, edema of lungs, enlargement of heart, irregular pulse, enlarged liver (dulness extending from fifth interspace to three fingers' breadths below costal

margin), edema of genitalia and extremities. At time of test liver was firm and tender and edge extended four fingers' breadths below costal margin. Patient developed bronchopneumonia and died. No autopsy.

No. 21, Med. No. 31988. M. V. W., aged sixty-three years, female, black, January 23, 1914.

Clinical Diagnosis. Diabetes mellitus, arteriosclerosis, perforating ulcer. Polyphagia, polydipsia, polyuria, and ulcer on right foot; duration ten months. On admission nothing striking except arteriosclerosis and ulcer on plantar surface of right foot at base of great toe. Liver not enlarged, not felt. Urine showed 15 gm. glucose on admission, which disappeared on a carbohydrate-free diet. No acetone or diacetic acid at any time. Gluscose reappeared on a full diet.

No. 22, Med. No. 31765. E. T., aged forty-five years, female, black, January 14, 1914.

Clinical Diagnosis. Arteriosclerosis, aortic, mitral and myocardial insufficiency, dilated aortic arch, chronic nephritis. Three previous admissions to hospital, the first in 1899 for acute rheumatic fever, the other two in 1911 and 1913 for symptoms similar to those of present admission. Dyspnea, swelling of legs and abdomen and nycturia, duration ten weeks. On admission signs of myocardial insufficiency, edema of lungs and extremities, ascites, enlarged heart (15 cm. to left and 4 cm. to right), liver edge felt three fingers' breadths below the costal margin, firm and rounded, tender. Albumin and casts constant in urine. Gradual improvement and decrease in size of liver under rest in bed and digitalis therapy.

No. 23, Med. No. 31870. M. B., aged sixteen years, female, white, January 6, 1914.

Clinical Diagnosis. Mitral stenosis and insufficiency, myocardial insufficiency, pulsus irregularis perpetuus. Frequent attacks of rheumatic fever, and attacks of palpitation of heart for eight years accompanied by swelling of feet. For two months gradually increasing swelling of abdomen and extremities with dyspnea and orthopnea. On admission signs of marked decompensation of heart, general anasarca, enlarged heart (17 cm. to left, 4.5 cm. to right), ascites sufficient to necessitate paracentesis. At time of injection liver flatness extended from sixth rib in mammillary line to below the level of the umbilicus. Compensation was never restored, and patient left hospital against advice of physicians. She was readmitted later because of return of symptoms.

No. 24, Med. No. 31904. C. B. H., aged sixty-two years, male, January 6, 1914.

Clinical Diagnosis. Arteriosclerosis, chronic nephritis, myocardial insufficiency, uremia. Dyspnea on exertion for nine months, weakness of legs and vague pains in abdomen. On admission Cheyne-Stokes respiration, cardiac dulness 15.5 cm. to left, marked atherosclerosis, liver not enlarged, hypertension (180 to 220), albumin and casts persistently present in urine,

Wassermann negative, phenolsulphonephthalein excretion, none at end of first hour, 15 per cent. at end of second hour. Patient was extremely restless and seemed on the verge of going into uremic convulsions, but under eliminative treatment he improved distinctly.

No. 29, Med. No. 31920. J. H., aged sixty-three years, male, white, January 6, 1914.

Clinical Diagnosis. Carcinoma of stomach, metastases. For four months pain in abdomen after eating or drinking, occasional vomiting and constipation, with loss of weight and strength. On admission patient showed emaciation, anemia, red blood cells, 3,520,000; hemoglobin, 46 per cent., and a mass in the epigastrium continuous with liver dulness. No jaundice, palpable liver, with nodular surface according to one observer. Occult blood in stools, no free hydrochloric acid in stomach juice. Wassermann negative, gastro-intestinal *x*-rays showed "gnawing out" of the shadow of the greater curvature, persisting in several plates and suspicious of carcinoma. Patient steadily lost weight and tumor in the epigastrium grew steadily larger. Death February 6; no autopsy. Prevailing opinion was carcinoma of stomach with metastases to liver.

No. 30, Med. No. 32458. W. N. J., aged forty-eight years, male, white, April 21, 1914.

Clinical Diagnosis. Carcinoma of stomach. For about twenty-four years patient has had abdominal pains before each meal, and five years ago an especially severe attack, since which time he has had weakness, loss of appetite, emaciation, pain in the epigastrium, occasional vomiting, chronic constipation, and edema of the ankles. On admission emaciation, anemia (red blood cells, 2,084,000; white blood cells, 8000; hemoglobin, 20 per cent.) and a palpable mass in the epigastrium, thought to be a carcinoma situated at the pylorus. Liver not thought to be enlarged. Gastric analysis showed sarcinæ, Oppler-Boas bacilli, white blood cells, subacidity, lactic acid, and occult blood. Bismuth *x*-rays showed pyloric obstruction and gastric retention.

No. 31, Med. No. 31971. C. H., aged thirty-nine years, white, male, January 24, 1914.

Clinical Diagnosis. Leukemia, splenomyelogenous. For three months patient had noticed slight fulness in left upper quadrant of abdomen, which has increased rapidly. On admission pallor, and enlarged spleen. Liver not palpable. Red blood cells, 4,448,000; white blood cells, 102,800; hemoglobin, 58 per cent. Differential count (Ehrlich), polymorphonuclear neutrophiles, 22.3 per cent.; polymorphonuclear eosinophiles, 4.7 per cent.; polymorphonuclear basophiles, 4.0 per cent.; small mononuclears, 3.3 per cent.; large mononuclears, 17.0 per cent.; transitionals, 10.3 per cent.; neutrophilic myelocytes, 27.3 per cent.; eosinophilic myelocytes, 5.7 per cent.; basophilic myelocytes, 3.7 per cent.; unclassified, 1.7 per cent.; normoblasts, 12 cells; megaloblasts, 17 cells. Wassermann negative.

Discharged April 6, 1914. White cells were reduced under benzol and *x*-ray therapy to 40,000 on discharge.

No. 32, Med. No. 31565. C. R., aged twenty-five years, male, white, October 10.

Clinical Diagnosis. Leukemia, splenomyelogenous. Enlarged spleen for two years, some pain in left side. Splenic dulness 25 x 35 cm. Liver dulness from fifth rib to one finger's breadth below costal margin; edge not felt. White blood cells, 229,000. Differential count: polymorphonuclear neutrophiles, 43.4 per cent.; polymorphonuclear eosinophiles, 3 per cent.; polymorphonuclear basophiles, 0.6 per cent.; small mononuclears, 0.6 per cent.; large mononuclears, 1.0 per cent.; transitionals, 0 per cent.; myelocytes: neutrophilic, 46.5 per cent.; eosinophilic, 1.1 per cent.; basophilic, 0.9 per cent.; unclassified, 1.6 per cent. Injected October 24, 1913, and January 6, 1914.

No. 34, Med. No. 31704. E. W., female, black, January 14, 1914.

Clinical Diagnosis. Pernicious anemia, gastric anacidity. For one year vague attacks of "indigestion," nausea and vomiting, and feeling of languor. On admission a slightly yellowish tinge to scleræ, marked pallor, moderate edema of the legs. Red blood cells, 1,198,000; white blood cells, 2960; hemoglobin, 24 per cent. Much anisocytosis and poikilocytosis. Monoblasts and megablasts seen. Gastric analysis showed absence of free hydrochloric acid.

No. 35, Med. No. 32312. J. E. F., aged forty years, male, white, March 26, 1914.

Clinical Diagnosis. Pernicious anemia, pyorrhea alveolaris. Periods of weakness, nervousness, "indigestion," and diarrhea for five years, increasing during the past year. On admission pallor, yellow skin, pyorrhea alveolaris, liver edge just palpable at costal margin, reflexes present. Red blood cells, 1,548,000; white blood cells, 6350; hemoglobin, 35 per cent. Marked poikilocytosis, anisocytosis, and variation in color of cells. One normoblast seen. Polychromatophilia. Gastric analysis showed absence of free HCl. Discharged after three weeks stay in hospital; no improvement in condition noted.

No. 36, Med. No. 32436. M. H., aged twenty-eight years, female, black, January 21, 1914.

Clinical Diagnosis. Syphilis (Wassermann). Syphilis of the liver. Ascites. Ventral hernia (incarcerated). Gradual swelling of abdomen eight months before admission; paracentesis six times in five weeks before admission; blood in stools on several occasions. On admission icteric tint to scleræ, glandular enlargement, ascites, hydrothorax, liver palpable three fingers' breadths below costal margin. Wassermann positive. Red blood cells, 4,640,000; hemoglobin, 60 per cent. Attempt made to aspirate pleural cavities; no fluid obtained. Calmette test positive, 5 per cent.; 6500 c.c. fluid removed at abdominal tapping. Subsequently patient

developed an incarcerated hernia and was operated upon by Dr. McClure. At operation liver was felt and found to be very hard and enlarged, to have a sharp edge and a slightly nodular surface.

No. 38, Med. No. 31900. C. C., aged twenty-seven years, male, white, January 6, 1914.

Clinical Diagnosis. Pleurisy with effusion, tuberculous peritonitis, pericarditis, adherent pericardium. Syphilis (Wassermann). Gradually increasing edema of ankles and swelling of legs for seven months, accompanied by some dyspnea, cough and abdominal pain. On admission patient showed marked orthopnea and dyspnea, jaundice (slight), tachycardia, marked ascites, edema of extremities, fever (105°), leukocytosis. After removal of 12.75 liters of fluid from the abdominal cavity the liver edge extended 6 cm. below the costal margin in right mammillary line and 8 cm. below the ensiform in median line. Surface was firm and slightly irregular. Tuberculin test (Calmette) positive. Wassermann positive. Ascites recurred necessitating repeated abdominal tappings. Later on fluid was removed from right pleural cavity. Patient maintained a remittent fever and died March 8. Urine negative. Clinically this patient was thought to have an advanced cirrhosis of the liver. At autopsy none was found. *Autopsy:* No. 4087. March 10. Anatomical diagnosis. Tuberculous peritonitis; adhesion of bowel to abdominal wall; paracentesis opening extending into it; ascites; adhesive pericarditis (tuberculous); cardiac hypertrophy and dilatation; collapse of both lungs; acute and chronic tuberculous lymphadenitis; tubercles of liver and spleen; chronic passive congestion of viscera; cloudy swelling of kidney, general anasarca, chronic pancreatitis (?). *Liver microscopically:* There are a few old scars made up of dense connective tissue which may be of syphilitic origin. No evidence of tuberculosis. The centres of lobules show a little atrophy of the liver cells with some fatty degeneration. There is a good deal of postmortem degeneration making it difficult to determine the condition of the liver cells. The main change can be explained by passive congestion of a moderate grade and there is no histological evidence of any other change which should interfere with the function. *Liver grossly:* Liver weighs 2300 gm. It is enlarged, measuring 28 x 19 x 9 cm. Its surface shows thick fibrinous exudate. This layer of exudate is hemorrhagic in appearance. When this is peeled off, the surface is left studded with small tubercles which are also reddish in color. There are also some dense fibrous adhesions between the under surface of the diaphragm and the liver. The cut surface is seen to be mottled dark grayish color with a rather prominent lobulation showing. However, on close inspection there is seen to be a definite congestion of the central areas with atrophy apparently and some hypertrophy of the liver substance about the portal areas. There are a few tubercles which can be made out definitely. In the left lobe of the liver there is a rather homogeneous boiled-like appearance,

as this portion of the liver has undergone rather rapid postmortem digestion. The demarcation line between this and the right lobe of the liver is quite distinct. Beside the congestion and definite tubercles being of apparent postmortem change there is nothing very remarkable about it. The atrophy and hypertrophy are secondary to the congestion. No definte cirrhosis.

No. 39, Med. No. 31742. J. W. D., aged forty-two years, male, November 25, 1913.

Clinical Diagnosis. Tuberculous pleurisy with effusion, peritonitis and pericarditis. Admitted complaining of dizziness, weakness and pains over heart, duration six weeks. On admission patient showed evidences of fluid in both pleural cavities and pericardial cavity, an enlarged liver, dulness extending from fifth rib to 6 cm. below the costal margin in the right mammillary line. Liver edge was palpable and there was shifting dulness in the flanks. Red blood cells, 4,152,000; hemoglobin, 61 per cent.; white blood cells, 5920. Patient maintained a remittent fever, temperature going as high as 103°, which gradually came to normal after rest in bed. Urine showed a trace of albumin from time to time; no casts.

No. 40, Med. No. 32139. A. L. W., aged forty years, male, white, February 20, 1914.

Clinical Diagnosis. Congenital hemolytic jaundice, ulcer of legs. Had malaria at twelve years, with jaundice and "ague cake" spleen; jaundice has persisted since. Since the age of sixteen he has had ulcers on the legs, which have healed and broken down again. He had three admissions to the hospital about thirteen years ago, at which time a diagnosis of splenic anemia was made. The eldest son (nine years old) of the patient has had jaundice for four years, no other symptoms. On admission jaundice of the skin and scleræ; palpable liver edge 6 cm. below the costal margin in the right mammillary line; enlarged spleen, and ulcers on the legs. Red blood cells, 3,504,000; white blood cells, 9250; hemoglobin, 70 per cent. Wassermann negative, after provocative salvarsan. Dr. George R. Minot stained the red blood cells vitally with brilliant crystal blue, and in 1500 cells counted found 5 per cent. reticulated and less than half of these showed large reticulæ. Calmette (5 per cent.) positive. Patient was seen by several observers, all of whom found enlarged liver and spleen as described above, in addition to the jaundice, and all of them thought that the case was one of congenital hemolytic jaundice. Studies of the blood, with regard to the presence of pigments, made by Dr. George R. Minot and Dr. C. G. Guthrie showed presence of bilirubin in the serum, but no definite evidence of urobilin in the serum. Urobilin and urobilinogen were present in the urine.

No. 41, Med. No. 32443. J. H. T., aged thirty-six years, male, black, April 23, 1914.

Clinical Diagnosis. Acute lobar pneumonia (right upper and lower). Syphilis (Wassermann). Four days before admission had malaise, weakness and giddiness, followed by chill, loss of appetite and cough with pain in the right chest, and difficulty in breathing. On admission signs of consolidation of right lower lobe, continued fever 104° to 106° and leukocytosis. Two days after admission he developed an intense jaundice, with bile in the urine. Liver dulness 2 cm. below costal margin. Stools not clay-colored. Course of disease uneventful except for occurrence of a delirium and rather slow resolution.

No. 43, Med. No. 32355. R. M. A., aged fifty years, male, white, April 18, 1914.

Clinical Diagnosis. Syphilis (Wassermann); tabes dorsalis; acute nephritis; chronic nephritis. Twenty-two years ago he had syphilis, treatment two years. Five years ago began to have lightning pains. Strabismus for one month. On admission inequality of pupils, internal strabismus of right eye due to paralysis of right internal rectus. Argyll-Robertson pupils on left, positive Romberg and slight ataxia on walking. K. K. absent. Blood-pressure, 184 to 120. Urine on admission showed a mere trace of albumin and no casts were found. Spinal puncture gave a clear fluid, 30 cells per cmm., slightly positive Noguchi, and a positive Wassermann. Wassermann in blood negative. Patient was given 0.3 gm. salvarsan intravenously and had no reaction afterward other than an increase in lightning pains. Five days later patient was given 0.5 gm. salvarsan intravenously, and about 30 minutes later had a chill and temperature rose to 106° (rectal), pulse became weak, and patient seemed dazed. Temperature remained high for two days; patient developed a blotchy, erythematous rash and urine contained a large amount of albumin and granular casts. Jaundice appeared, pulse failed, and patient died three days after the intravenous salvarsan. *Autopsy:* No. 4109. April 18. Tabes dorsalis (intravenous salvarsan); diffuse central necrosis of liver; jaundice; acute splenic tumor; acute glomerular nephritis; subserous hemorrhages; duodenal ulcer; chronic gastritis; arteriosclerosis; chronic orchitis. Liver weight 1500 gm. The surface is normal. On section the lobulation is distinct, the centres being of a brick red and the margin of a yellowish color. Microscope: shows central necroses associated with fatty degeneration affecting at least one-half of each liver lobule. The degenerated liver cells are partly dissolved and being removed by phagocytes, which are numerous in these areas. The remaining liver tissue shows a good deal of fatty degeneration but many normal liver cells. Great numbers of mitotic figures are found in the hepatic epithelium, indicating rapid regeneration following injury. The connective tissue is nowhere increased and the picture resembles that seen in chloroform poisoning. With a liver lesion of this extent the output in the dog would be decreased to less than one-half normal and might be much lower even.

No. 44, Med. No. 31496. M. S., aged forty-nine years, male, white, October 24, 1913.

Clinical Diagnosis. Peripheral neuritis, bronchial asthma, eosinophilia, pentosuria, pyorrhea alveolaris. Paroxysms of asthma for two years, loss of weight and increased frequency of micturition. Liver edge palpable 1 cm. below costal margin. Wassermann negative. White blood cells, 26,000. Eosinophiles, 83 per cent. Pentose in urine.

No. 45, Surg. No. 33712. J. S., aged forty-seven years, female, white.

Clinical Diagnosis. Gall-stone in common duct. For six years had recurrent attacks of abdominal pain, and for three months before admission she had continuous dull pain in right hypochondrium. Jaundiced for a week before admission to hospital. On admission patient had jaundice; slight prominence in right hypochondriac region; liver edge palpable 2 cm. below costal margin; spleen palpable; 13,000 leukocytes; bile in urine; acholic stools, and slight fever. At operation a stone was found in the common duct, adherent to the mucosa, and the common duct was widely dilated, about 3 cm. in diameter, and containing a great quantity of bile. The stone was removed, a small catheter placed in the common duct, with the end toward the liver, a drain was placed in the gall-bladder and the wound closed.

DISCUSSION ON PAPERS OF DRS. BROWN, WHIPPLE, AND ROWNTREE, MARSHALL, AND CHESNEY

Dr. A. E. Taylor: Referring to the paper of Dr. Brown, I venture to discuss several technical features of studies with the diastatic ferment which, in my experience, are of crucial importance in the application of the test. All ferments are sensitive to bacterial action, and though this diastatic ferment is less sensitive than many, still it is sensitive. It is absolutely essential that the stool to be examined shall be relatively recent and represent recent pancreatic secretion, as a negative result in a particular stool may mean inactivation or non-secretion by the pancreas. For practical purposes it is not safe to trust a negative result unless the secretion analyzed is less than twenty-four hours old. This has been realized in the general use of purgation, but this alone is not sufficient. In perfectly normal individuals, who are not constipated, who have a daily normal stool of normal consistency, the colonic habits are different, and the stool of Sunday may represent the food of Saturday, Wednesday or Thursday. In other words, if we administer stool markers, we may recover the marking in twenty-four, forty-eight, seventy-two, or even ninety-six hours; and if to such an individual an ordinary purge be administered, one may recover only the lower contents of the colon, one may not recover the marked stool for thirty-six or forty-eight hours after the purge acts. With the

ordinary purge of cascara, castor oil, or sodium phosphate, it is necessary not only to practice purgation, but to mark the stool also. If purgation brings out the marked stool within twenty-four hours, the test for diastase may be applied to the stool.

Dr. C. P. Howard: In our clinic, Dr. C. W. McClure made a thorough test of diastase in the urine and feces and came to this conclusion, that the normal variation was so great that no possible application to pathological conditions could be made, and we have rather discarded, therefore, this test, just as we have the Cammidge reaction. After a study of 103 normal pancreatic controls, he found a variation in the feces of 0 to 5000 units, and in the urine, from 2 to 200 units. Wohlgemuth's technique was followed to the letter.

Dr. Wilder Tileston: I have made a number of determinations of trypsin and diastase in the feces in cases of pancreatic diseases, using the Cross casein method for the former and the Wohlgemutt method for the latter. My experience has been that the trypsin test gives far more reliable information than the diastatic one. The theoretical objection to casein is that it is digested to some extent by eropsin, an intestinal ferment, but in practice the cases where the pancreatic duct has been completely obstructed have shown very low values for trypsin, and the results have been confirmed by autopsy in several cases. In the case of the amyolytic ferment, however, I have found low values where the trypsin content was normal and there was no reason to suspect disease of the pancreas.

Dr. L. F. Barker: I think Dr. Brown's study has shown the clinical value of this test. He has emphasized the great importance of a standardized technique and he has pointed out that diastase is very susceptible to external influences. One particular influence that is worth noting is that of the salts of the feces. It has been shown that after the stool has been subjected to dialysis to remove the salts, there is no diastase-activity at all; since the salt content of the feces varies considerably it may be wise to follow the suggestion of H. Rotky (Prog. med. Woch., 1913, xxxviii, 413 and 414) in order to obtain more exact results.

Dr. Alfred Stengel: In connection with the examination of the stool for ferments to determine pancreatic disease, my experience of removing the pancreatic secretion or duodenal contents with the Einhorn tube has been uniformly satisfactory. I see little need of the examination of the stool with all the possible difficulties with such a test. I have had some cases in which it has been impossible to obtain the duodenal contents because the capsule did not pass through the pylorus; but these failures have been exceptional in a number of cases, perhaps a score or more. I

have taken the duodenal contents in cases of pancreatic disease and tested them for ferments to determine their presence in quantity or absence. Some have experienced difficulty in getting the Einhorn capsule to pass through the pylorus, and this difficulty has arisen in those individuals who have taken considerable food. If considerable food has been taken this method will not give good results, but if, after a test-meal of purely liquid food, such as broth, or something like that, is taken, it will pass almost invariably and the duodenal contents can be obtained. That is a great advantage over the method Dr. Brown has presented, because there is less danger of the admixture with saliva, because, although there is created great salivary secretion by swallowing the tube, the passage of the tube through the pylorus is relatively rapid and the pylorus is shut very tight, so that one can determine by drawing off the duodenal contents and withdrawing the tube. It seems to me, this method of obtaining duodenal contents is more thorough and superior to examining the stools for these ferments.

Dr. Brown (closing): I did not give the exact details of the method. My plan is to give a laxative the morning before, an enema the evening preceding, and a light evening meal. After the milk at 7 A.M., the laxative at 7:30 and 8 A.M. At 8:30 I give a glass of water and some bicarbonate of soda; the stool up to 2 P.M. is carefully examined, it having been kept in an ice-box. The lower bowel is irrigated with normal salt solution, if less than 400 grams has been eliminated. The difference in the bacterial content and psyche are errors that cannot be absolutely eliminated. The method I have outlined, with an absolutely rigorous technique, and immediate examination of the stool, will, I think, be found to be a reliable test. Our experience has been that if we wait seven or eight hours we get all the diastase response by the method employed. It does give a low normal limit which is of assistance in the diagnosis of certain diseases as verified by this group of cases of chronic pancreatitis and carcinoma.

With regard to the methods for testing the function of the liver reported by Dr. Rowntree, I think that every clinician has been impressed with the difficulty of studying the liver functionally. Of all large glands in the body, we know least about the liver and its functions. The clinicians must be grateful for the series of comparative tests which Dr. Rowntree has made and reported here this morning. Many of them are difficult tests. They are elaborate and require an extensive laboratory technique. Many will be disappointed at the small practical clinical yield as yet obtained from these tests. But the outlook for the future is promising. Intensive studies such as those reported, may lead sooner or later to the setting out of entirely new clinical syndromes, corresponding to hepatopathies which at present we know nothing about.

A DIFFERENTIAL STUDY OF COCCIDIOIDAL GRANULOMA AND BLASTOMYCOSIS

I. PATHOLOGY AND BACTERIOLOGY
II. REPORT OF TWO ADDITIONAL CASES OF COCCIDIOIDAL DISEASE

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To California physicians who have seen a good deal of a disease peculiar to the San Joaquin Valley and described as coccidioidal granuloma, there seems to be a confusion on the part of some writers as to its relation to blastomycosis and, indeed, it has been frequently referred to as one and the same disease. It is our purpose to show how real the confusion is in the literature, and by describing the morphology of the two organisms, their development and appearance in tissue as well as the reactions found, and finally by comparison of the effect of each form on inoculated animals, to show that they are distinctly different and not merely different forms of the same organism with different methods of development and different toxicity under varying conditions. This latter view is held by Wright, who in his article on the subject in Osler's *System* regards all the cases reported under the names coccidioidal granuloma and blastomycosis as different manifestations of the same disease which he calls oidiomycosis. He states that the prognosis is bad where the condition is due to infection with sporulating forms, whereas only four of thirty cases died where infection was with budding forms. He discusses briefly Wolbach's

morphological studies and animal work with the sporulating forms, and considers the budding forms another phase of the same organism.

Whitman, who studied a case of "systemic blastomycosis" in Denver, recognizes the confusion which exists, and in an article on the "Botany of the Organism of Blastomycosis" states "the organisms in these cases are probably not identical." The importance of budding referred to by many authors as a differential morphological characteristic is set aside by him as having no biological significance and no longer used by mycologists on account of its being found so widely distributed among fungi. "There is apparently ample ground for the view that the term 'blastomycosis' really includes a wide variety of organisms. Cultures from different cases present considerable variations in morphology and cultural characteristics." An abundance of budding forms marked some, whereas an absence characterized others. Some recovered rapidly under potassium iodide, whereas others progressed obstinately in spite of it.

In his case Whitman states, "I have observed for the first time the production of mycelia within the tissues." He traces the development of asci in the tissues, stating that budding forms are exceedingly rare. He concludes that the plant may belong to the Monascaceæ or Exoascaceæ in the ascomycetes group, and that a study of the behavior of this organism under conditions natural to the life of related groups would possibly give complete information regarding its botanical position.

Brewer's case of an abscess in the back, connected with the lumbar vertebræ, was studied by Wood, who reported the pus showing large numbers of spherical cells of different sizes (10 to 25 micra), each surrounded by a clear gelatinous envelope. No budding was found in the organisms as seen in fresh pus, and mycelia were not observed in cultures which grew easily but slowly on ordinary media.

Zinsser discussed the morphological characteristics of the organism found in Brewer's case of blastomycosis. Unlike most forms described, his organism grew poorly on all fluid media. Reproduction was by budding, and in no case even in agar and gelatin hanging

drops were mycelia observed. In old cultures daughter cells grew and budded again without detachment entirely from the mother cell.

Ewing in the discussion reported a case in Coley's service from which an organism with abundant mycelia was cultivated. The organism grew at room temperature and even in the ice-box.

Irons' and Graham's cases of generalized blastomycosis showed no special points of interest except the belief that the primary lesion was in the lungs. Although they state, as is generally believed, that dissemination is by the blood stream, two blood cultures were sterile. Cultures on ordinary media showed elevated, mold-like, definitely margined growths with aërial hyphæ and mycelia. Budding forms were found in young cultures.

Morris, of New York City, reports as systemic blastomycosis the case of a physician from Texas who infected his finger the year before while dissecting in Chicago. MacNeal and Hjelm, who made the cultures and discussed the diagnosis in the same journal, describe the organism as growing, after forty-eight hours' incubation, in "radiating mycelial threads." The fresh pus contained double contoured spheres (4 to 25 micra). No budding forms or mycelial threads were recognized in the pus, but in growths the mycelia were abundant. They regarded the organism as "identical with that discovered by Posada and Wernicke and first described in the United States by Rixford, who bestowed on it the name Coccidioides immitis.

Buschke in vol. v, pp. 155-210, of Kolle und Wassermann's *Handbuch der path. Mikroörganismen,* discussed at length the "Hefeähnliche Microörganismen." In the oidiomycetic infections of tissue he states that the oval bodies alone are found, mycelia having been observed by no authors. Gilchrist's disease he calls Oidiomycosis Americana and the coccidioidal granuloma cases of Ophüls and Moffitt and other American authors he regards as the same affection. He would group them under the heading of blastomycosis.

A detailed review of literature on coccidioidal disease and blastomycosis has not been attempted by us. Ricketts presented an exhaustive study, in 1901, of the clinical and laboratory aspects

of the disease and concluded that the so-called "protozoic disease" (coccidioides) of Posadas, Wernicke and Ophüls, and Gilchrist's blastomycetic dermatitis were various manifestations of the same disease. He described the lesions of blastomycosis consisting of subcutaneous abscesses or granulomatous nodular growths with usually the appearance of a primary papule. The abscesses had a cauliflower-like surface with elevated borders and surrounded by a red indurated zone. The centres of the lesions showed granulations. Marked epithelial hyperplasia was noted, as well as epidermal and subepidermal abscesses. Dense infiltrations of cells, including giant cells, were noted. Vast numbers of organisms were found in some cases in the pus and granulation tissue. In the viscera small nodular masses and abscesses with and without cheesy material developed. A comparative study of the organisms, including blastomycetes or oidiomycetes and the organism of Ophüls and Moffitt's "so-called protozoic disease," revealed practically no differences. At least there appeared to be no greater differences than between the various strains of his blastomycetes. Most of the organisms developed on artificial media in one or two days, certain others requiring two to seven days. He divided the entire group (including Busse's "Saccharomycosis hominis" and Curtis' "Saccharomycosis humaine") into three classes, depending upon the appearance of growth on culture media: (1) elevated, moist, white colonies coalescing to form a fleshy growth of paste-like consistency; (2) granular surface, slightly elevated and upon coalescing more elevated and eventually surface looking like a piece of crumpled cloth or mass of earth worms; (3) aërial hyphæ and surface white, dry, and flour-like, and eventually covering sides of the container. Some of the organisms produced acetic acid, some fermented glucose and maltose, and others fermented saccharose and lactose, while others had no fermentative activity. One produced indol. A complete study of the "protozoic" organism appears not to have been made. Experimental inoculations showed considerable resistance to infection by the various strains of blastomycetes on the part of guinea-pigs, dogs, and rabbits.

In 1904 Wolbach studied a strain of coccidioidal organisms isolated from a patient with subcutaneous lesions. Growth

appeared in culture media in two to seven days, and after some time it showed on solid media an opaque white, elevated centre due to aërial hyphæ bearing gonidia. In broth globular, white, thistle-down like masses developed and settled to the bottom of the tube. Saccharose, dextrose, and mannite were not fermented. Microscopically, the growth showed radiating masses of coarse, branching, segmented mycelia with distinct membrane. In very old cultures spherical bodies were found resembling those found in tissues. The organism was highly virulent for guinea-pigs and rabbits, and the lesions simulated tuberculosis. Endogenous reproduction was found in the organisms recovered from the animals. No evidences of mycelia nor budding processes were noted, although the latter were in some instances simulated owing to juxtaposition of the cells. The development of mycelia from the endosporulating cell as found in pus was studied on agar slides and hanging-block preparations and the reverse development by intravenously inoculating rabbits and examining sections of organs from twenty-four hours up to several weeks, as well as by the introduction of cultures sealed in collodion capsules into the peritoneal cavity of rabbits. Wolbach stated "that the organism cannot be a blastomyces, neither can it be included in the oidium-like group of Ricketts, since the organisms of that group may reproduce by budding."

In 1907 Hektoen published a detailed review of cases, and concluded that they were different diseases. In 1908 Montgomery and Ormsby summarized the literature, and in 1909 Harter published a book on blastomycosis.

In the *Archives of Internal Medicine* for April 15, 1914, a series of eleven case reports on systemic blastomycosis appeared together with a pathological, bacteriological, and clinical study of the disease by Stober. He obtained cultures from the moldy wood in the homes of the patients and noted a similarity with the cultures from human tissues. Vaccination with blastomycetes was tried on two systemic and one cutaneous case, of which one of the former recovered. The vaccine consisted of the filtrate and suspension of the triturated membranes of old bouillon cultures which had been heated at 110° C. He inclines to the theory that systemic blastomy-

cosis is primarily a respiratory infection. Blood cultures in a case reported by Krost, Stober and Moes were positive. (Buschke had previously reported one such case.) The urine also showed blastomycetes, the source of which, as shown at necropsy, was the prostate. This series of articles are reproductions from the Cook County Hospital reports, 1910, as noted on page 509 of the *Archives*.

The latest summary of recently reported cases of coccidioidal granuloma, together with experimental work has been published by MacNeal and Taylor. Anërobic cultivation of the "coccidioides immitis" in sterile ascitic fluid and gelatinized horse serum with pieces of sterile tissue showed upon inoculation of pus the development of spheres and no filaments at the bottoms of the tubes. Such cultures have been kept alive for three weeks. Their work supports the observation of Wolbach's that the double contoured spheres in the animal tissues develop by a direct transformation of septate mycelial threads and not from the chlamydospores, and that one point of practical therapeutic differentiation is the value of iodides in blastomycosis and their failure to benefit cases of coccidioidal disease as emphasized earlier by one of us (Brown). MacNeal and Taylor conclude that coccidioidal granuloma is a very definite specific infectious disease, and that "coccidioides immitis (class Ascomycetes) is distinctly different from the budding fungi found in human disease variously called blastomycosis, oidiomycosis," etc.

The association of coccidioidal granuloma and blastomycosis as one disease has been asserted by Wright, Ricketts, Buschke, etc., and a clinical confusion specifically illustrated by Morris' case of reported blastomycosis, which was shown on laboratory examination to be coccidioidal disease. Welch believes that they are two differentiable diseases, and Ophüls, Hektoen, Wolbach, MacNeal and Taylor, etc., have the opinion, as the result of clinical and laboratory observations, that they are separate conditions.

Personal Observations

Case I.—H. D. V., aged twenty-four years, San Joaquin Valley, California. Family and previous history negative. He was in Southern Pacific Hospital from August 16 to 20, 1912, for laryngitis, which was

suspected of being tuberculous, although reactions were negative. Readmitted with typhoidal symptoms. Widal positive, 1 to 40, and blood-culture negative. Died Mach 2, 1913, having been in hospital about two months. Gross examination of organs revealed apparently a disseminated miliary tuberculosis, while microscopically coccidioidal lesions were found in the spleen, lungs, liver, kidneys, pancreas, and adrenals. The organisms showed endosporulation. There were no cultures. (Carson and Cummins, *Jour. Amer. Med. Assoc.*, 1913, lxi, 191.)

Case II.—Service of Dr. S. J. Gardner. J. P., aged twenty-nine years, Mexican, laborer in section gang (railroad), Bakersfield, San Joaquin Valley, California, was admitted to hospital July 27, 1913. Family history was negative. Denied venereal infection. The present infection apparently began three weeks before admission with a nodule on the dorsum of the right great toe. The day before admission it had been lanced and a quantity of pus escaped. He denied injury.

Examination. Poorly nourished adult. Temperature was 104° and only a slight increase in respiratory and pulse rate. Head, chest, and abdomen negative. Right great toe presented two open wounds, which were exuding considerable pus. Throughout the course of the disease the temperature fluctuated between normal and 104°. The foot was kept for varying periods of time in a salt-water bath, and potassium iodide was administered internally in 20-grain doses thrice daily. There was no improvement, and the patient was transferred to the roof that the foot might be exposed to the direct sun rays. For a time there was some decrease in the amount of pus. However, there was progressive decline, and about two weeks before death he became stuporous, and had by this time become markedly emaciated. There were no apparent joint or other bone lesions and no evidences of pleurisy. No cough.

Pus from toe showed typical coccidioidal organisms with endosporulation. Tissue from margin of lesion showed the same. Blood: August 9, hemoglobin, 70 per cent.; red blood cells, 4,760,000; white blood cells, 16,600. Blood cultures: August 6 and September 15 sterile. Urine: July 29, negative. Wassermann reactions: blood serum, August 2 negative, and cerebrospinal fluid, September 10, weakly positive (++). The fluid was moderately turbid and under a pressure of 140 mm. Butyric acid and ammonium sulphate reactions positive. Cells 20 (?) per cubic millimeter. Death occurred September 16.

Postmortem Record. Markedly emaciated body. Bed-sores over sacrum. Peritoneum smooth and dry and no adhesions. Spleen moderately enlarged (240 grams). There were numerous small, firm, grayish nodules of millet-seed size. Liver slightly enlarged (1620 grams), dark brown, and flabby. Gall-bladder apparently normal as well as stomach. Intestines were moderately congested. Pancreas apparently normal. Both kidneys moderately enlarged (200 to 210 grams). Several millet-seed

sized, whitish areas in cortex and medulla. Adrenals, ureters, bladder, and genitalia apparently normal. Left pleural sac showed few, rather firm adhesions at apex. Lung (500 grams) showed numerous closely aggregated, grayish, firm nodules throughout both lobes. Right pleural sac normal. Lung (620 grams) resembled the left. Heart (300 grams) had a pale, flabby muscle. Valves apparently normal. Beginning of aortic arch showed few small areas of early sclerosis. Retroperitoneal lymph nodes were moderately enlarged and firm. Brain (1360 grams) showed a uniformly moderate thickening of the dura mater. Overlying the occipital dura there was a well-defined purulent collection which was directly continuous through a necrosed portion of the occipital bone with a larger mass of pus beneath the scalp. There was early necrosis of the left temporal bone. There was extensive necrosis of the upper half of the sternum and the third, fourth, and fifth lumbar vertebræ with pus development, as well as the bones of the right great toe.

Microscopic examination showed coccidioidal lesions (endosporulating organisms) in the lungs, liver, kidneys, occipital bone, dura mater, meninges of cervical and dorsal cord; as well as congestion, edema, emphysema, and hemosiderosis of lungs; passive congestion of liver, congestion of adrenals, chronic gastro-enteritis, chronic retroperitoneal lymphadenitis; hyaline changes in right soleus muscle.

Cultures made at autopsy and incubated at 37°C. showed within twenty-four hours growth of coccidioidal organisms.

Case III.—Service of Dr. J. H. O'Connor. A. R., aged twenty-seven years, blacksmith helper, Kerto (since August, 1913), San Joaquin Valley, California. Admitted to hospital March 5, 1914. Family and previous personal history negative. Denied venereal infection. The present condition apparently began ten days ago with lumbar pains. *Stated that he lost about thirteen pounds in fifteen days.* He denied injury.

Examination. Fairly well-nourished man. On admission temperature, pulse, and respiration normal. No tenderness in lumbar region. Blood-pressure: systolic, 120 mm. Urine, negative. Two days after admission there was definite localization of tenderness, and a mass noted in the lumbar muscles over the left kidney. On opening there exuded considerable pus in which double-walled endosporulating cells were found. Six weeks after admission, tenderness and swelling of the right wrist and left elbow appeared. At that time there was a moderate purulent discharge from the lumbar lesion, whose walls were of a gray, slimy, necrotic appearance. Röntgen picture showed no apparent connection with spine. Throughout the period of illness an irregular temperature was maintained. Maximum was 103.4°. Daily applications for five minutes of gauze saturated with pure phenol were made over a period of seven weeks. Then for four weeks daily applications to the lesion of gauze saturated with 0.25 per cent. solution of crystal violet were made. At no time were there

evidences of granulations nor, on the other hand, extended necrosis. During the latter period intravenous injections of crystal violet were given as follows: May 8, 100 c.c. of 0.25 per cent.; May 11, 100 c.c. of 1 per cent.; May 16, 100 c.c. of 2 per cent.; May 19, 400 c.c. of 4 per cent. Slight chills following three injections were probably induced by insufficient heating of the solution rather than by any toxicity of the crystal violet. On May 13, 5200 c.c. of violet-tinged ascitic fluid were withdrawn; May 21, 2250 c.c.; May 28, 1040 c.c. The swelling of the wrist and elbow decreased, and there was no other apparent bone or joint involvement. Death occurred June 1. Unfortunately permission for autopsy could not be obtained.

Experimental Work. The coccidioidal cultures used for animal inoculations and bacteriological study were those from Case II; the blastomycosis culture was obtained from a systemic case at the City and County Hospital through the courtesy of Dr. Harold Hill. A limited bacteriological study has been carried out on the strain of coccidioides from Case III. Other cultures of coccidioides have been obtained from Dr. Cook, of the University of California, and from Drs. MacNeal and Taylor, of the Post-Graduate Medical School in New York City, and form the basis of study which is not yet completed. Rabbits, guinea-pigs and white rats were inoculated with the coccidioides and blastomycetes, and cats with the coccidioides only.

Animal Experiments (Coccidioides)

five rabbits

A—December 13. Inoculated intravenously 2 c.c. salt solution suspension culture containing spores.

December 29. Killed. Coccidiosis of liver. No evidence of coccidioidal disease.

B—December 13. Intraperitoneally, 5 c.c. salt solution suspension of culture.

December 29. Killed. Coccidiosis of liver. No evidence of coccidioidal disease.

C—December 13. Intrapleurally as A.

December 16. Negative.

December 22. Negative.

January 5. Pea-sized mass near site of inoculation, but not attached to ribs.

January 23. Chestnut-sized mass.

April 4. Killed. Large mulberry form abscess intrathoracic at site of inoculation. Small abscess extrathoracic. Left ankle-joint enlarged and contained some pus; at right knee small firm tumor. Coccidioidal organisms in pus.

D—December 13. Intratesticularly (right) as A.

December 16. Small bead at epididymis.

December 22. Both testicles enlarged and right indurated.

January 5. Sinus from right.

January 23. Both testicles size of small lemons. No discharge from sinus.

February 28. Killed. Purulent orchitis (bilateral), coccidioidal organisms in pus.

E—December 13. Inguinally (right) as A.

December 16 and December 22. Negative.

January 5. Split-pea sized nodule in groin.

January 23. Lima-bean sized nodule at seat of inoculation.

March 18. Killed. Purulent arthritis, left shoulder and right elbow. Pus showed coccidioidal organisms.

Resumé. Intrapleurally, intratesticularly and in inguinal region positive. Intravenous and intraperitoneal inoculations negative.

NINE GUINEA-PIGS, MALE

A—September 3. Inoculated intraperitoneally 2 c.c. salt solution suspension of pus from Case II.

September 22. Both testicles somewhat enlarged.

October 2. Sinus from each testicle.

October 21. Killed. Coccidioidal lesions of testicles and spleen.

B—Inoculated as above.

October 2. Indurated ulcer of scrotum.

October 29. Also enlarged right inguinal nodes.

December 4. Testicle healed: inguinal enlargement persisted.

December 16. Died. Coccidioidal involvement of inguinal nodes only.

C—September 3. Inoculated as above.

September 27. Both testicles somewhat enlarged.

October 7. Small indurated ulcer of scrotum.

October 29. Also enlarged inguinal nodes both sides.

December 4. Killed. Large mass in left inguinal region. Some enlargement of axillary groups in both sides. Coccidioidal disease present.

D—November 24. Inoculated 4 c.c. salt solution suspension four months' old culture intraperitoneally.

December 4. Some induration of both testicles.

December 12. Also slight inguinal enlargement.

December 16. Died. Coccidioidal lesions in left inguinal node and testicle.

Resumé. Intraperitoneal inoculations positive.

E—F—G—H—December 18. Each inoculated intraperitoneally with 1 c.c. salt solution suspension pus from "D" pig testicle.

December 21–22. All died. Congestion of lungs, liver, kidneys, and adrenals. Cultures from peritoneal fluid sterile.

I—December 21. Inoculated intraperitoneally 1 c.c. salt solution suspension of peritoneal exudate from one "December 18 pigs."

December 25. Died. Congestion of heart, kidneys, lungs, and liver. Cultures from peritoneal fluid sterile.

THIRTEEN WHITE RATS

A—September 6. Inoculated subcutaneously in back with 1 c.c. salt solution suspension pus from Case II.

March 22. Ulcer at site of inoculation.

October 2. No pus; more induration.

October 19. Died. Negative.

B—C—September 6. Inoculated intraperitoneally as above.

September 14. Some redness and swelling at site of inoculation.

October 2. Some induration testicles.

November 12. Negative.

January 20. Killed. Negative.

D—November 24. Inoculated intraperitoneally with salt solution suspension four months' old culture.

December 4. Small nodule at site of inoculation.

January 5. Negative.

April 4. Killed. Small firm cysts in liver. Coccidioides in smears and cultures.

E –F –G—March 5. Inoculated intraperitoneally with 1 c.c. salt solution suspension of pus from testicle of rabbit "D." March 17. Killed, and one only showed coccidioidal organisms in fluid from small hepatic cyst.

H—I—J—March 5. Inoculated as above.

April 17. Killed. All negative.

K—L—M—March 5. Inoculated testicularly as above.

April 17. Killed. All negative.

Resumé. Two of thirteen rats, positive.

FIVE CATS

A—Full grown.

September 5. Inoculated intraperitoneally 2 c.c. salt solution suspension pus from Case II.

September 14, 18, 27, and October 2. Some swelling at site of inoculation.

October 15 and 22. One area size of quarter-dollar piece and several smaller areas.

November 15. One large area of induration.
December 4 and 12. Small nodule.
January 5. Negative.
January 28. Killed. All organs grossly negative. Microscopically, few coccidioidal organisms found in small dense cellular collections in lungs.
B—Full grown.
September 5. Inoculated subcutaneously in back, as above.
September 14, 18, 27 and October 2. Some swelling at site of inoculation.
October 7. Small area of induration.
October 22. Area of fluctuation.
October 29. Ulcer. Coccidioidal organisms in smears.
November 5. Ulcer healing.
December 4. Ulcer healed.
December 12. Negative.
January 28. Killed. Few small whitish nodules in liver. Smears negative. Other organs including brain and cord grossly negative. Microscopically few coccidioidal organisms in lungs as above.
C—Kitten.
September 14. Inoculated intraperitoneally 2 c.c., as above.
January 28. Killed. All organs grossly and microscopically negative.
D—Kitten.
September 18. Inoculated intraperitoneally as above.
September 22. Negative.
September 27 and October 2. Two pea-sized masses at inoculation site.
October 7 and 22. Moderate increase in size.
November 15. Negative.
January 28. Killed. All organs negative grossly and microscopically.
E—Kitten.
September 18. Inoculated subcutaneously in back. At above dates of examination negative.
January 28. Killed. All organs negative grossly and microscopically.
Resumé. Full-grown cats, positive. Kittens, negative.

Blastomycetes

four rabbits

1—December 13. Inoculated intraperitoneally 5 c.c. salt solution suspension of five months' old culture.
December 16 and 22. Negative.
January 5. Abdomen somewhat boggy.
January 23. Killed. No evidence of blastomycosis.
2—December 13. Inoculated inguinally as above.

December 16. Negative.

December 22. Died of pneumonia. No evidence of blastomycosis.

3—December 13. Inoculated intrapleurally with 5 c.c. as above.

December 22, 23, January 5, 23, and April 16. Negative.

April 17. Killed. No gross evidence of blastomycosis.

4—December 13. Intratesticularly (right) with 0.75 c.c. as above.

December 16. Some swelling of testicle.

January 5. Testicle as large as a lime.

April 16. Apparently normal.

April 17. Killed. Tunica vaginalis testis contained two split-pea sized nodules containing thick pus in which blastomycetes (budding forms) were found. Right lower eyelid was covered with thick pus and small papillar projections were noted when pus was removed. Blastomycetes were found in pus.

Resumé. Intratesticular inoculation, positive. Intrapleural, inguinal, and intraperitoneal inoculations negative.

THREE GUINEA-PIGS, MALE

1—November 24. Inoculated intraperitoneally with 4 c.c. salt solution suspension of four months' culture.

December 22. Boggy abdomen.

December 26. Died. Congestion of liver and kidneys. Abscess in right epididymis containing drop of pus. Blastomycetes in smears and cultures.

2 –December 27. Inoculated intraperitoneally with 2 c.c. salt solution suspension of pus from guinea-pig's "1" epididymis.

January 13. Died. Congestion of lungs and liver; acute nephritis; acute follicular splenitis. No blastomycetes.

3—Inoculated as 2.

April 17. Killed. No evidence of blastomycosis.

Resumé. Two of three intraperitoneal inoculations negative.

WHITE RATS

1—November 24. Inoculated intraperitoneally with 2 c.c. salt solution suspension of four months' old culture.

December 4. Small nodule at site of inoculation. Killed April 4. Negative.

General Summary of Animal Inoculations. White rats seem to be markedly insusceptible to infection with coccidioides and blastomycetes; cats to coccidioides. Rabbits and guinea-pigs appear to be more susceptible to coccidioidal and blastomycetic infection.

Guinea-pigs and white rats showed a tendency toward localization of the coccidioidal and blastomycetic infections, while rabbits showed disseminated lesions of the former and localized lesions of the latter infection. No lesions were found in the cerebrospinal tissues. Passage through animals would seem to exalt the virulence of coccidioides as shown by five guinea-pigs (E-I).

Cultural Studies. Both coccidioides and blastomycetes grew well on agar of strongly acid and alkaline reactions. Dextrose, dextrin, lactose, saccharose, maltose, raffinose, mannite, galactose, aesculin, sorbit, agaricin, rhamnose, adonit, xylose, arabinose, mannose, and salacin were not fermented by the coccidioides or blastomycetes. The addition of potassium iodide to media for facilitating the growth of the coccidioides or blastomycetes, by inhibiting the growth of contaminating bacteria, was not employed in the isolation of the organisms from pus, as it was found that after a short time they overgrew the bacteria.

It was noted that the blastomycetes tubes incubated at 37° C. did not grow so well or as rapidly as when they were kept at room temperature. This fact has been called attention to by Ophüls, whose further statement that coccidioides grow best at 37° C., we also confirm.

Of fifty dyes in neutral agar the violets uniformly showed the greatest inhibitive action on the coccidioides, blastomycetes and staphylococci and the greens ranked second. The blue dyes varied considerably from the strongest, methylene blue BX and brilliant cresyl-blue to the weakest, trypan blue and china blue. Such dyes as safranin, congo red and victoria blue showed well-marked differences in their action upon the respective organisms. A relatively marked inhibition was effected by safranin on staphylococci. The reverse was true of congo red. Victoria blue exerted a well-marked inhibition of the growth of blastomycetes and no inhibition on the coccidioides and staphylococci; purpurin, orange G, rubin S, sudan III, methyl red, etc., were quite inert. (Some poorly soluble.) Uniformly the most inhibitive dye was crystal violet, but for the blastomycetes methyl violet I B and 6 B. Crystal violet and Hoffman's violet were of equally high potentiality for the coccidioides and blastomycetes. Intraperitoneal inoculations of aqueous solutions of crystal violet in 0.25, 0.5, 1

TABLE I.—Reactions of Staphylococci, Blastomycetes and Coccidioides with Various Dyes of Different Strengths.[1]

VIOLET DYES		0.0005	0.001	0.0025	0.005	0.01	0.02	0.05	0.1	0.25	0.4	0.5	0.6	0.75	0.9	1.0	1.25	1.5	1.75	2 c.c.
		0.01%	0.02%	0.05%	0.1%	0.2%	0.4%	0.1%	2%	5%	8%	10%	12%	15%	18%	20%	25%	30%	35%	40%
Cresyl-Echt-violet	B	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−
	C	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−
	S	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−
Crystal violet	B	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	S	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Dahlia	B	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	S	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Gentian violet	B	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	S	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Hoffmann's violet	B	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	S	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Methyl violet 1 B	B	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	S	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Methyl violet 2 B	B	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	S	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Methyl violet 5 B	B	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	S	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Methyl violet 6 B	B	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	S	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Methyl violet Bx	B	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	S	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Rosanilin violet	B	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	S	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

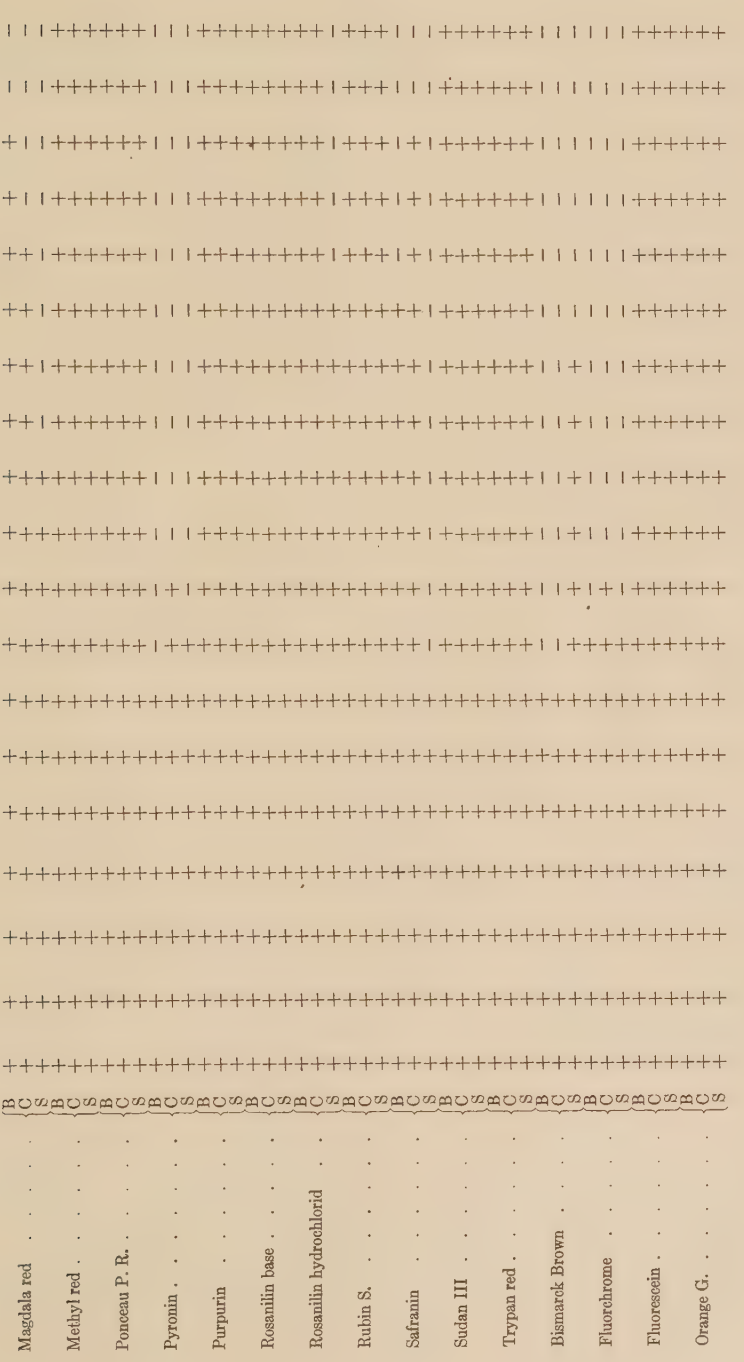
[1] Explanation of abbreviations in table: B, blastomyces; C, coccidioides; S, staphylococcus (from a case of osteomyelitis). 5 c.c. neutral agar per tube. Saturated aqueous solution of dyes from which serial percentages (0.01 to 40) were made. Tubes autoclaved for twenty minutes.

GREENS
Brilliant green
Emerald green
Iodin green
Janus green
Malachite green
Methyl green
BLUES
Anilin blue
Brilliant cresyl blue
China blue
Methyl blue
Methylene-blue Bx
Methylene-blue, med. pur.
Methylene-blue, rectif.
B
C
S

TABLE I (Continued).

		0.0005	0.001	0.0025	0.005	0.01	0.02	0.05	0.1	0.25	0.4	0.5	0.6	0.75	0.9	1.0	1.25	1.5	1.75	2 c.c.
		0.01%	0.02%	0.05%	0.1%	0.2%	0.4%	0.1%	2%	5%	8%	10%	12%	15%	18%	20%	25%	30%	35%	40%
BLUES																				
Nile blue sulphate	B[1]	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	S	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Toluidin blue	B	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−
	C	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−
	S	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−
Trypan blue	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Victoria blue	B	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REDS																				
Carmin rubr. opt.	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Congo red	B	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−
	C	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−
	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Corallin water	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−
	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
Eosin watery blue	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Erythrosin	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−
	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−
Fuchsin basic	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−
Hematoxylin	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	C	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	S	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−

[1] Explanation of abbreviations in table: B, blastomyces; C, coccidioides; S, staphylococcus (from a case of osteomyelitis). 5 c.c. neutral agar per tube. Saturated aqueous solution of dyes from which serial percentages (0.01 to 40) were made. Tubes autoclaved for twenty minutes.


B C S
Magdala red
Methyl red
Ponceau P. R.
Pyronin
Purpurin
Rosanilin base
Rosanilin hydrochlorid
Rubin S.
Safranin
Sudan III
Trypan red
Bismarck Brown
Fluorchrome
Fluorescein
Orange G.

and 2 per cent. concentration into guinea-pigs and white rats produced no toxic effects. As before noted, this dye was made the basis of therapy in Case III.[1]

The primary growths of the coccidioides from Cases II and III, required two to ten days for their appearance, except in the former where a few tubes of slant agar were thickly streaked with pus, and growth appeared within twenty-four hours. There is a tendency primarily for the pyogenic organisms to outstrip the coccidioidal growth, but in the course of two weeks the former growth is practically obliterated. After several subculturings of strain II growth appeared in twenty-four hours. This strain showed the initial characteristic of fine, white threads radiating out over the agar surface, while that from Case III showed a whitish "cottony" surface without such radiations. As the agar slants became covered with growth both strains assumed a somewhat dry, wrinkled, fleshy, brownish-white appearance. Especially in strain II there was early penetration of the agar, and in the thinner, drier portions of the media (top of slant) there was an early development of the whitish "cottony" growth. This appearance was not general until the cultures became old and dry.

Strain III has not been studied sufficiently long to determine this point. In both strains the growth after a time was of irregular thickness, being in places somewhat elevated and densely adherent to the media, so that it was necessary for subinoculation to remove small pieces of agar. Strain II on the "dye-agars" developed in many tubes well-marked aërial hyphæ as a primary growth. With some dyes, notably eosin, orange G and the rosanilins, general growth was more rapid and luxuriant than on the plain agar. Those cultures developed early the whitish, dry, "cottony" growth, in dense masses, projecting from the surface of the medium. All tubes were incubated at 37°C.

Early in the period of subculturing our strain of blastomycetes, seven to ten days elapsed before there were evidences of growth, but later in many tubes this period was reduced to two or three days. The primary growth in all plain agar slants, consisted of

[1] "Safraninagar" in 10 to 20 per cent. strength may prove of value in the isolation of coccidioides from pus and in 10 to 15 per cent. strength, in the isolation of blastomycetes.

round, moist, flat colonies composed of radiating, whitish lines. Later, coalescence took place, and the surfaces dried and cultures assumed the appearance as described by Ricketts "(3) aërial hyphæ and surface white, dry and flour-like and eventually covering sides of tube." For subinoculation, this growth could easily be removed without puncturing the agar. The "eosin," "orange G," and "rosanilin" agars favored luxuriant growths. On practically all of the "dye agars" primary growth was manifested by aërial hyphæ. All tubes were kept at room temperature.

Microscopically, both the coccidioides and blastomycetes in animal tissues presented the characteristic endosporulation and budding processes, respectively. Neither in the pus, nor in the solid tissues at any time could we demonstrate budding forms in coccidioidal disease, nor evidences of endosporulation in blastomycosis. No mycelia were found in the tissues in either disease. In cultures of both types of organisms, the already well-described cylindrical, septate, branching filaments with later spore development, were noted. Agar slides, as described by Wolbach, were used to study the development of filaments from the cells as found in pus. We found the most satisfactory stain of the culture material to be eosin and methylene blue, but in pus the cells were readily studied upon adding a dilute (4 per cent.) caustic soda solution.

The initial growth of coccidioides on culture media is rapid, for, if a quantity of pus is inoculated, some growth is noted within twenty-four hours. Blastomycetes require in their initial growth about ten days to two weeks for evidence of definite development, but after prolonged cultivation growth is seen in four to seven days. The optimum temperature for coccidioides is 37° C., and for blastomycetes about 20° C. Some strains of blastomycetes eventually show luxuriant growth to the extent that the sides of the container are invaded, whereas the growth of coccidioides seems always to be confined to the media.

Animal inoculation yielded well-defined endosporulating organisms of coccidioidal disease, and in the pus of blastomycosis only the budding forms, *vide supra.*

There appear to be sufficient reasons to justify the consideration of coccidioidal disease and blastomycosis as two different diseases.

A second paper will deal with the diseases from serological, vaccine, and chemotherapeutic stand-points.

Summary. There are well-defined differences in the pathogenicity of the two diseases, coccidioidal granuloma being always fatal, and often rapidly fatal, in man, while blastomycosis is commonly not so, except for the systemic cases, in which the organisms were found associated with bacteria of known and unknown pathogenicity (Zinsser, Hektoen, Gilchrist and Stokes). The clinical and pathological aspects of coccidioidal disease are those more clearly resembling tuberculosis, as there is a greater predilection for the lymphatic system than there is in blastomycosis, and cutaneous lesions are likely to be more ulcerative. There appears but one reported case of coccidioidal disease in the female sex, whereas there have been many of blastomycosis. Iodides have temporarily benefited many, and apparently cured a few cases of blastomycosis, whereas, they have had no effect upon the slowly, but usually rapidly, progressive lesions and toxemia of coccidioidal granuloma.

In the reported cases of coccidioidal granuloma and blastomycosis, confusion is common as to clinical, pathological, and bacteriological characteristics. The two organisms appear closely related, having much in common but with such differences as to justify the conclusion that they are distinct entities. Morphologically, in pus and solid tissues, they are differentiable by the endosporulation in the one and budding in the other. Cultural differences are not so pronounced, although we have found that growth is initially more rapid with coccidioides. Blastomycetes appear to grow best at room temperature (20° C.); coccidioides at 37° C. The table of dyes shows some differences in the inhibition of growth.

Rabbits and guinea-pigs are more resistant to blastomycetic than coccidioidal infection.

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DISCUSSION

Dr. William H. Welch: I think this is an extremely welcome study of the origin of these two affections. I have been interested in this subject ever since the study of the first case in my laboratory after the brief communication of Chiari. We studied side by side the first two cases of coccidioidal disease and the material sent by Dr. Duhring, of Philadelphia, of blastomycetic infection. We were impressed then with certain tests described in the article written by Gilchrist and Richardson. As bearing out Dr. Cummins' statement, I will say that the resemblance of the coccidioidal affection to tuberculosis was most striking; whereas in the blastomycetic affection the tendency to small miliary abscesses was remarkable. The diagnosis in general is made by the microscopic examination of sections and secretions, endogenous sporulation in one without budding, and in the other the budding form.

I would like to ask Dr. Cummins if the localization of the disease in California remains, as I supposed it to be, in the San Joaquin Valley and Sacramento Valley, and whether it has spread to other parts. Nearly all cases came from that region in the Middle West, and the great majority of cases are due to budding blastomyces. I have no doubt that he is correct, that in these blastomycetic affections we have a variety of parasites.

Dr. Cummins (closing): In answer to Dr. Welch, as far as we know the cases in our hospital have been confined to the San Joaquin Valley. I would like to add that I am quite sure Dr. Welch agrees with us in believing they are two separate pathologic conditions.

ON THE DIRECTION OF RESEARCH AS TO THE ANALYSIS OF CORTICAL STIGMATA AND FOCAL LESIONS IN CERTAIN PSYCHOSES[1]

By E. E. SOUTHARD, M.D.
OF BOSTON

I DESIRE to bring before this Association certain points and viewpoints in theoretical psychiatry, trusting to be able to persuade the Association members that the task of finding genetic factors in psychiatry is not absolutely hopeless. I know that psychiatry and, indeed, the entire field of neuropathology in its most general sense are looked on as hardly germane to practical medicine. Yet the members of this Association, while not willing to go on the witness-stand (as did the Philadelphian of legend) as *general specialists*, should be among those who would see the general connections of psychiatry most clearly.

Since 1906 I have been making, collecting, and tabulating observations, largely from postmortem data, which bear on theoretical psychiatry and more especially on genetic factors.[1] Naturally my data have been largely somatic, both neural and non-neural, although by turning special attention to cases without obvious brain lesions I have latterly developed some hypotheses about the so-called functional psychoses. [2 3 4 5]

After paying some attention to the frankly and admittedly "organic" psychoses (general paresis[6] and other syphilitic mental

[1] Being contributions of the State Board of Insanity No. 42 (1915.8).
Bibliographical note: The previous contribution (1915.7) was by Rose S. Hardwick, entitled "Programs and Directions for the Mental Examination of Asocial, Psychopathic, and Doubtful Subjects," to be published in the Boston Medical and Surgical Journal, 1915.

diseases, and arteriosclerotic and senile atrophic conditions),[7] [8] I found most of my research interest passing to the region of the so-called functional psychoses, viz., to dementia precox[9] [10] (which, to be sure, is now beginning to be regarded in many quarters as "organic" in some sense) and to manic-depressive insanity[11] (about whose anatomy Kraepelin could say, in 1913, "there are no certain data"). I entered the investigation of these functional psychoses with the definite prejudice that nothing relevant would be found anatomically in the brains—that is, no evidence of lesion entailing permanent damage and cell-loss. Perhaps prejudice is too harsh a word for such a method of approach, since I hold that a brain, like an alleged criminal, should be considered normal (that is, innocent of lesions) until proved not so.

However that may be, the brains of dementia precox subjects, selected at random and examined in sufficiently large number, proved to exhibit certain anatomical appearances of a very intriguing nature. These appearances may perhaps be called lesions if the term lesion can be used to include both acquired lesions and the results of germ-plasm taint, embryonic and fetal factors, and such early acquired lesions as seem almost tantamount to antenatal lesions. But these lesions and stigmata, occurring in a large majority of cases of dementia precox (the larger, the more careful the analysis, as I have since shown by systematic photographic analysis), are exceedingly hard to analyze as to their genetic significance. On the whole I was impressed with their large significance as indicators of hereditary, congenital, or acquired weak places in the brain structure, finding as I did histologically that whereas the construction of the tissue might be faulty (anomalous architecture) there was superadded evidence of progressive disease entailing cell-loss and characteristic tissue reactions (scavenger functions of Bevan Lewis, supportive neuroglia proliferations of Weigert, etc.).

But, while the significance of such lesions as indicators of past and present disease must be provisionally accepted, it is not so clear that the particular symptoms of dementia precox can be safely correlated with the particular lesions found. Indeed, I suppose it would be unwise to count all dementia precox phenomena as essentially paralytic or postparalytic phenomena (in the sense of Hugh-

lings-Jackson), and dependent upon fine cell-losses, in that it was not likely that the principles of the old extirpation-neurology even when extended to finer anatomy, were to carry us far into the field of essentially irritative phenomena which so many mental symptoms and conditions assuredly are. Meantime, I have made certain correlations between site of lesions and character of symptoms that seem to me to hang together (frontal lobe lesions and delusions of ordinary type,[9] [10] [12] parietal lesions and catatonia,[9] [10] temporal lesions and auditory hallucinosis[10]). My argument does not here concern these correlations, although the cases mentioned below will involve some of them.

Restricting inquiry to the nature of such lesions and not dealing with their effects, let us ask the more general question, What is the relation of these lesions to dementia precox in general? Before approaching this question in detail, we must ask whether such lesions are found in other diseases. Do not normal persons possess them? And, even if they do not show acquired lesions superadded, may they not show anomalies of such sort and with such frequency as to make such lesions quite non-characteristic for dementia precox? It is curiously hard to answer this question and, from the literature, almost impossible. I have data partly analyzed from general hospital autopsy series from which I believe I am safe in asserting that no great number of the brains of sane persons possess such anomalies. But a more positive answer, and one to my mind quite convincing, is derived from an exact analysis of the brains of subjects of that other functional psychosis mentioned above, viz., manic-depressive insanity.

Here I find, instead of four brains out of five showing coarse evidence of brain-disorder (as in dementia precox), but one brain in five showing such brain-disorder in manic-depressive insanity. (Let me insist that the criteria were the same for both series and that the confusing issues of arteriosclerosis were excluded to the same degree from both series by leaving out cases with lacunar lesions due to vascular plugging.)

These two sister affections, dementia precox and manic-depressive insanity, in fine stand upon entirely different bases with respect at least to the gross visible and tangible effects of cell-loss. And

these findings are to be held as roughly correlatable with the different curabilities of the two affections, since the outcome of dementia in dementia precox is held to be characteristic and the tendency to recovery or to restoration of a symptomless condition is characteristic of manic-depressive insanity.

It is perhaps necessary to remark that these anatomical observations do not necessarily imply that the microscope will not discover lesions (and genetically important lesions) not related to anomalies and not issuing in sclerosis or atrophy. All we can say is that such lesions are unlikely to be anything but what logicians might call reversible; they would be lesions unlikely to result in cell-losses of any great proportion.

If I am asked why my figures are not absolute, why the fifth dementia precox brain does not show gross lesions and why the fifth manic-depressive brain does show gross lesions, I have several pertinent answers. (1) Our clinical diagnoses are not accurate to 100 per cent., although they possibly should be more accurate than 80 per cent. (Even the clinical accuracy of diagnosis in general paresis did not surpass 85 to 90 per cent. until very recent years, and with diagnostic devices nowhere approached in delicacy in the field here in question.) (2) Our anatomical diagnoses, especially those embodied in our protocols, are not always accurate. This has been emphasized in my recent photographic studies, wherein important anomalies are repeatedly shown which had been quite overlooked on the autopsy table. (3) Our conceptions of the two diseases are not entirely clear. Sometimes I get the impression that the distinctions drawn are to some extent upon false lines, although I do not doubt on present evidence that Kraepelin has arrived at a rough approximation to the truth.

Again, the microscope may come to our aid. With respect to dementia precox, I have recently found two cases of very brief duration in which elaborate photographic analyses of the gyri yielded no sign of gross lesion, but microscopically there was the most abundant and convincing evidence of neuroglia proliferation and cell-pictures decisive of the fact of cortical disease. Was there in these cases no long-standing cortical anomaly, and, had the cases lived, was the disease process finally to discover weak places in

the cortex such that topical scleroses and atrophies would supervene? or were these brains in process of a generalized mild atrophy? *Quien sabe?*

With respect to manic-depressive insanity, we are to some extent, aided by the current view that all of the characteristic clinical phenomena of manic-depressive insanity may occur in virtually any other form of insanity, since the manic-depressive phenomena are really only quantitatively different from the reactions of the normal man. If this is the case, we might easily believe that a case with a brain marked by an anomaly signifying a potentially weak place could still have symptoms such as a manic-depressive would have. Hence, a few cases might come through to autopsy with anomaly-bearing brains but with symptoms not at all related thereto.

However this may be, the fact of these differences remains in the tale of gross lesions which we can collect from these two sister affections. No one can deny, except on the basis of more penetrative analyses than my own, that dementia precox brains look abnormal much more often than do manic-depressive brains. But are these abnormalities inborn or acquired? And, even if not inborn, are some of them perhaps acquired so early that they interrupted development seriously at a period long prior to the appearances of symptoms? Are they, in short, anatomical appearances running *pari passu* with the course of symptoms, or are they rather *nidi* for the incubation of symptoms.

This is a question to which no general answer could or should be given. In the first place it cannot be said that either dementia precox or manic-depressive insanity is an absolutely well-established entity. In fact the entifying of these conditions will largely depend upon dicta of the postmortem room, the microscope, and the test-tube.

There are three sets of microscopic data which have attracted attention in analyses of dementia precox brains. There are (*a*) data concerning products of degeneration inside and outside of neurones.[13] There are (*b*) data concerning neuronophagia or satellitosis.[14] And there are (*c*) data concerning cell-losses. Probably the best-known work, at least with the two former groups of data, is that of Alzheimer, and it may be surmised that the data concerning

cell-losses given in Kraepelin's systematic account of dementia precox[15] (1913) are largely, if not entirely, based on descriptions by the same esteemed master of neuropathology.[16] Those of us who have enjoyed more or less work in Heidelberg or Munich are also aware how far these developments have been favored by Nissl.

The Nissl-Alzheimer school has, however, not made the same progress with dementia precox as with general paresis, largely, I suppose, for the technical reason that no such almost pathognomonic cell as the plasma-cell in paresis has been found to aid the tyro in the histological diagnosis of dementia precox. It was as early as 1897 that Alzheimer first called attention to the phenomenon now known conveniently as satellitosis in the cerebral cortex of catatonia.[14] That proliferation of neuroglia cells, especially in the lower layers of the cortex, had been thus found, was the chief contention of structuralists for their view of dementia precox. But with the lapse of time this contention has lost some of its force, partly because many cases failed or were said to fail to show satellitosis, partly because interest shifted to other matters (especially degeneration products), and partly because the conclusion has apparently been arrived at that infrastellate (lower-layer) gliosis is not so characteristic as suprastellate (upper-layer) cell-losses in the cortex of dementia precox.[15]

Accordingly, whereas the Heidelberg and Munich workers have persistently clung to a structural theory of the pathology of dementia precox, yet it cannot be said that they have clung to it consistently, as the basis of the claim has now been satellitosis, then *Abbauprodukte*, and again cell-losses.

Not being myself able to see anything differential in these different findings, I chose another line of attack and made careful topical examinations of the cerebral cortex in dementia precox,[9] hoping to show topical variations in the degree of whatever non-differential cell-changes might be going on and thus to determine the areas that suffered most. My efforts struck me as having a certain success. And I note that Kraepelin, whose structural notes for the volume published in 1913 evidently did not contain a reference to my work of 1910, has approximated my conclusions of 1910, basing his own upon an analysis of cases published by various hands.[16]

I do not, however, feel that enough work has been done to render any of these conclusions absolutely safe.

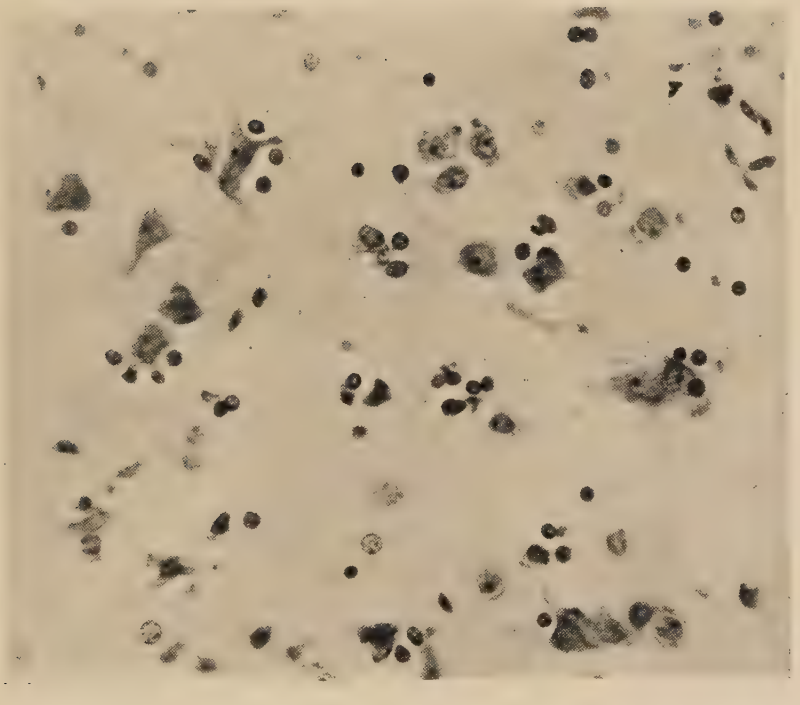
Tentatively in my own work I regard the degeneration-products of Alzheimer, or Marchi degeneration-products (non-Wallerian forms), or the iron-hematoxylin-staining substances with which I have personally worked,[7 17 18] as decidedly not differential for dementia precox. I understand Alzheimer to maintain that somewhat the same picture can be got in the tissues of a case of toxic delirium as in those of a catatonic *Hirntod*. The time relations of the appearance, fastigium and disappearance of these degenerative products remain to be established.

Satellitosis I find myself regarding as equally non-differential and as developing somewhat more slowly and at all events lasting much longer than the *Abbauprodukte*. There is, I believe, doubt in some minds whether the appearances of satellitosis are ever erased. Some unpublished observations which I have been making with experimental monkey poliomyelitis material indicate that satellitosis may disappear within measurable periods. But it is clear that satellitosis remains a striking phenomenon far into the period of demonstrable cell-loss, and it is probable that the phenomenon is closely related with some of these cell-losses, whether as furnishing an active agent of destruction or as responding to chemical stimuli from the dying cells.

These three characteristic appearances, then, may perhaps be regarded as representing roughly successive histopathological phases in various degenerative diseases; but these phases may overlap and indeed be all present at the same time. But, from a combination of the phenomena, tentative conclusions can be drawn as to the order of events. Probably the least reliable of these sets of data is the degeneration-products, since it would appear that it is signally difficult to exclude terminal intoxications of one sort or other in cases dead of dementia precox or of any other mental disease. I have even been at some pains to show the extent of these possibilities in systematic cultivations of bacteria from the cerebrospinal fluid in several hundred cases.[19 20 21 22 23] In the absence of satellitosis and cell-loss the degeneration products taken by themselves would seem to be open to suspicion, unless they are extremely

DESCRIPTION OF PLATE I

Plate I illustrates cellular gliosis, in this instance chiefly *satellitosis, i. e.*, proliferation of those non-fibril producing neuroglia cells found normally in small numbers (usually not more than a pair) next to certain large nerve cells. Specimen from infrastellate layers of postcentral gyrus in a case thought to be dementia precox, dead at seventeen after two months' symptoms. There was no gross lesion of the brain in this case.



marked in a bacteriologically negative case such as that reported by my colleague Orton.[23] In any event it is probable that the soaking of tissues with *Abbauprodukte* is to some, or even to a large extent usually a reversible process, and that after a time little or no more evidence of such deposits can be seen than of the pneumonic exudate after recovery.

In order to bring to a point my tentative stand toward the matter of satellitosis and of cell-loss and toward their significance, I wish to present samples of histological data from two cases. It would appear that the considerations turning upon these may prove of still greater value in future analysis of similar material of which I now have a large collection.

I choose two areas of the cortex of which we know comparatively a good deal—the occipital region and the post-central gyrus.

To illustrate a point concerning the occipital region, I take a case already reported[9] (as Case VI). I shall not here repeat the facts concerning this case other than to say that the patient died at the age of fifty-seven years, after perhaps thirty-two years of a mental disease regarded as the paranoid type of dementia precox, in which disease there were a number of striking features. It is noteworthy that the brain, which weighed 1490 grams at death, showed no signs of atrophy to the naked eye, although there seemed to be tangible evidence of induration of the brain substance so that on the autopsy table the diagnosis of generalized cerebral sclerosis was made. It was also noted—and this is particularly striking in connection with the findings microscopically—that the occipital lobes felt firmer than the rest of the brain. There was nowhere any evidence of chronic change in the pia mater except over the superior frontal gyrus of each side. Microscopically, it may be noted in passing that we found a considerable degree of change in numerous areas. Particularly under the thickened pia mater of the frontal region there was evidence of fibrillar gliosis. Incidentally, there was found a gliosis of the cornu ammonis (it appears that there was one episode of olfactory and gustatory hallucinations of an unpleasant character; these were also associated with visual hallucinations, also unpleasant).

The most striking thing in the case was the patient's description

of peculiar spiritualistic phenomena, with "forerunners and communications." I take the following from the description:

> Patient would often communicate with God, assuming a rigid position, gazing into space, and saying, "God, our Heavenly Father, I would like to communicate, if convenient, don't discommode yourself?" He pauses a few moments and then says "Is that you? Is that really you, Heavenly Father? Please come as an apparition, as strong as you can;" then in a faint voice, "That's pretty good, pretty good. Can you come a little stronger, I wish you would if you could; that's pretty good, that's good. God, Heavenly Father, is it safe to show the forerunner in the face of Dr. Mitchell? Are you sure, perfectly sure? All right." He would then make a peculiar movement of the hands which he alleges is a forerunner and has the power of destroying life. Asked to forecast the future, he calls up God as previously and says, "I wish to ask a question in regard to Dr. Mitchell's success in the future? Is your time precious, God? Can you spare it?" He turns to examiner and says, "He is gone now to examine. He explains by astronomy." In the meantime, patient converses pleasantly about the weather until God calls, and later assures examiner that his success is to be unlimited and that he has received communication. Result of these communications was, as a rule, optimistic.

Of course, it is *a priori* most unlikely that any correlation could be found between the specific content of combined and, as it were, *scenic* hallucinations of this type with microscopic findings. It is nevertheless, very striking that the tangible evidence of gliosis found in the gross brain was most marked in the occipital area. Accordingly, I examined with considerable interest the tissues from this region. It is, of course, true that our methods of gauging the amount of gliosis are still in their infancy. What I have been tempted to trust to, rather than the finer methods of very recent years, is evidence of neuroglia cell increase or such highly marked nerve cell loss that no one could fail to be convinced by evidence offered. *Satellitosis*, that is, proliferation of non-fibril producing so-called satellite neuroglia cells (found normally in small numbers, as a rule not more than two, at the base of certain nerve cells) is a fairly striking phenomenon when exhibited as in Plate I. (See description of plates.)

There remains some doubt what satellitosis, or cellular gliosis, of this particular type actually means. Satellitosis signifies in part

at least what the older term *neuronophagia* was intended to mean, except that the term *satellitosis* does not indicate that the cells are engaged necessarily in a phagocytic process, or are in any sense actively devouring fragments or products of nerve cells. Nevertheless the satellites proliferate very probably under definite chemical conditions next to the nerve cells, and it is the belief of some authors that this neuroglia cell proliferation is an index of a degree of cell or tissue loss.

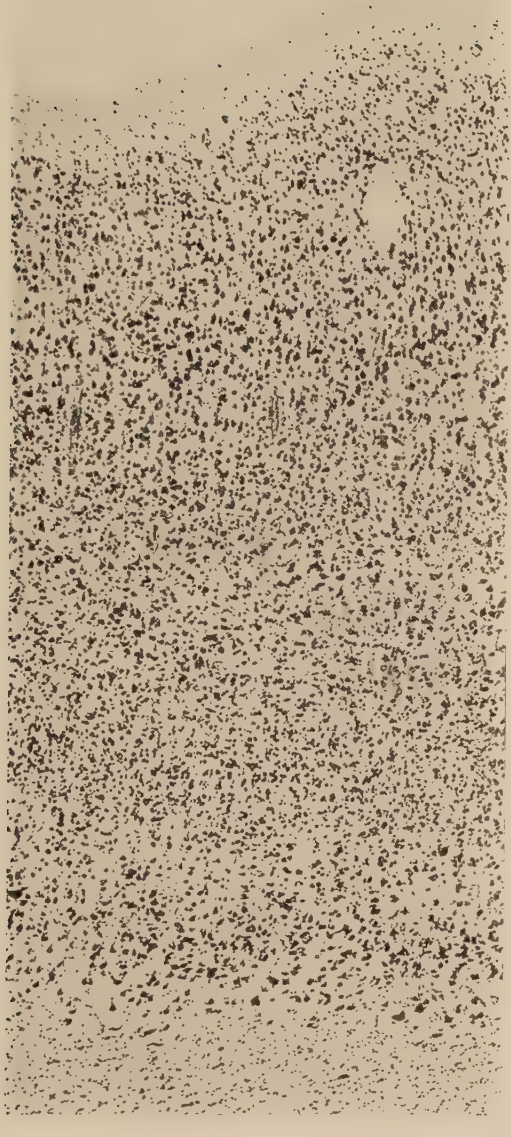
To return to the case of dementia precox just cited as having peculiar spiritualistic phenomena. A microscopic examination of the occipital cortex must consider both the type of cortex called "calcarine" and found in association with the white line of Gennari (or of Vicq d'Azyr), and the type of cortex which may be termed "common occipital," which surrounds the calcarine type, lying in general forward thereof. It is true that the mapping of this region by the topographers, Bolton, Campbell, Brodmann, and others, has not definitely decided what the still further anterior limits of the common occipital type of cortex are. But from the present more modest stand-point of histopathological analysis, it suffices to consider that there are very definite and easily observable distinctions between the two types of cortex which will readily permit us to draw conclusions as to the differential nature of lesions found in the two cortex types. In Plate II, a portion of the calcarine cortex is displayed which may not be in all respects normal, but at any rate fails to show evidence of cell loss, and with a hand lens one fails to discover convincing evidence of satellitosis such as that shown (with higher powers of the microscope) in Plate I.

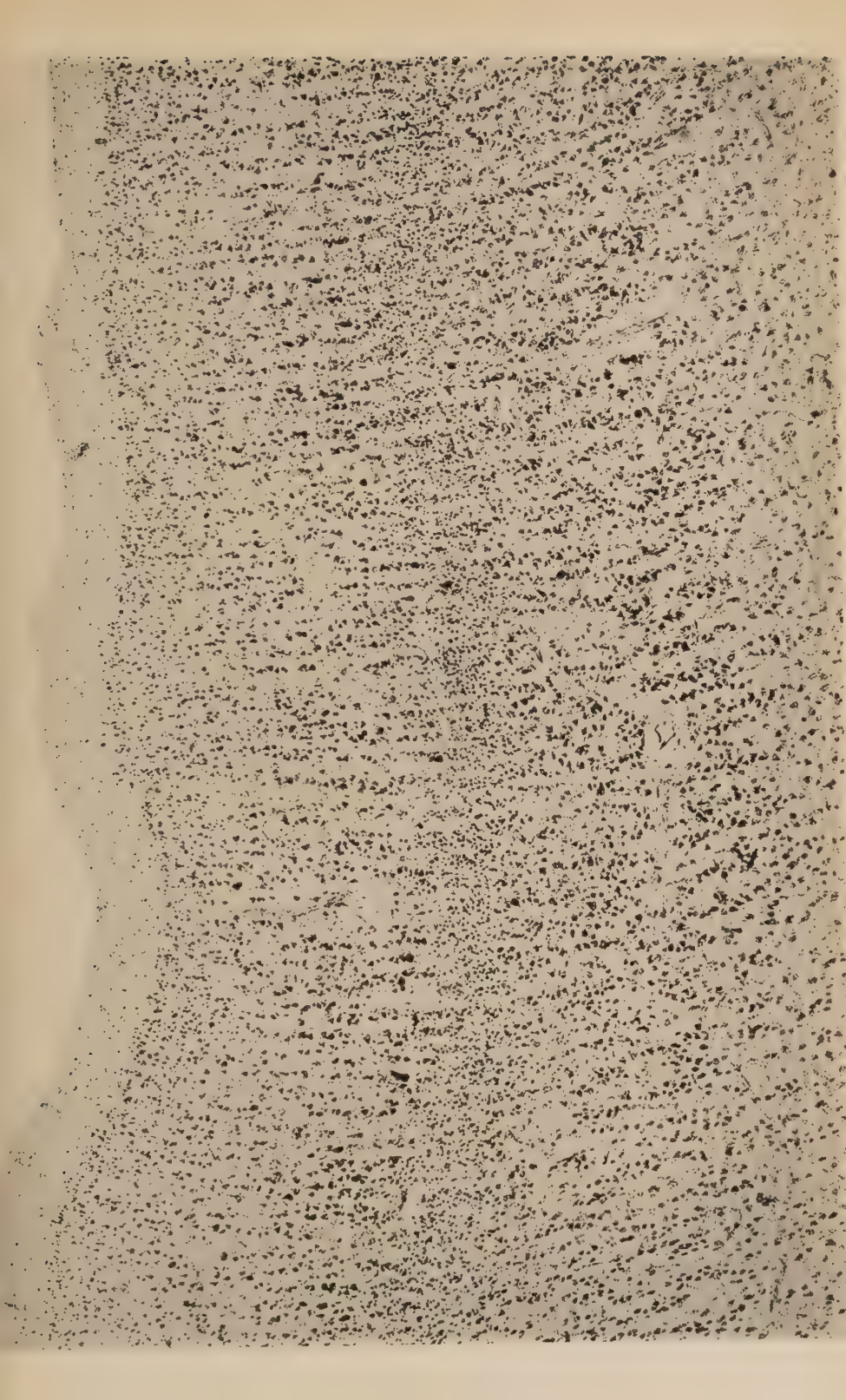
In Plate III, however, from the same case, and from the same block of tissue fixed and prepared by the same technique, observation with the hand lens will readily show in the lower part of the photograph numerous neuroglia cells, many of them in close relation to nerve cells. Most of the cell increase here shown is in the infrastellate layers, namely: in the lower half of the section as photographed; but traces of the change are also to be found in the suprastellate layers.

The argument from a comparison of appearances in Plates II and III is plain. Disregarding for the moment whether either

DESCRIPTION OF PLATES II AND III

Plates II and III are from a single microscopic preparation (alcohol fixation, original Nissl method, unimbedded) of the occipital cortex of the "spiritualist" victim of dementia precox with recurrent semivoluntary visual hallucinations. Plate II illustrates the calcarine or "visuosensory" (Bolton) area and does *not* show satellitosis. Plate III (from common occipital or so-called "visuopsychic" area) shows well-marked satellitosis (of general type resembling that shown in high power in Plate I), especially in the lower or infrastellate layers. There is also demonstrated the normal sharp differentiation between "visuosensory" and "visuopsychic" cortex. The pathological point turns on the satellitosis confined to the "psychic" area.





area is entirely normal in all other respects, it is certainly clear that the two areas are different in their content of satellite and neuroglia cells. I will not stop to inquire, moreover, into the question of the original quota of neuroglia cells in the two types or cortex. Future research may show that the common occipital type of cortex is better prepared with neuroglia cells than is the calcarine type. Even if this be true, it is still plain that the two regions must differ in their histopathological reaction to agents of like nature.

If I now add that the occipital pole is perhaps better understood than any other single area of the cerebral cortex with respect to its coarse functional relations, namely, the higher processes of vision, and if I add that all the work of the topographers above mentioned seems to show that the calcarine area is more of an arrival platform for impulses coming directly up from the thalamus and similar inferior sources, whereas the common occipital type of cortex is very probably more of an elaborative, associative, and combining nature, then I shall have made clear the general trend of my argument. If the visuo-sensory (calcarine) area has one sort of histopathological tendency, and the visuo-psychic (common occipital) type of area has another sort of reactive power, then it is clear that a toxin or chemical or physical, or other condition acting equally upon the two areas is nevertheless very likely to produce unequal results therein.

To sum up regarding the case of the spiritualist, it is unlikely that the appearances in Plate III are precisely responsible in any sense for the "forerunners and communications" of the case. But it is clear that by such methods, we shall be able to get a much more intimate insight into special conditions of the cortex and to discover special labilities of particular areas. As in future, physiology, comparative anatomy, and pathology, throw more light on special functions of areas, the meanings of these special liabilities of different cortex types will become clearer and clearer.

I now proceed to the discussion of a less well understood area, namely, the postcentral gyrus. To be sure, concerning the postcentral gyrus, we all remember the striking demonstration of Sherrington, who proved conclusively that the electric excitability

DESCRIPTION OF PLATES IV AND V

Plates IV and V contrast with low magnification the appearances in coordinate portions of the left (larger) and right (smaller) postcentral gyri in a case of catatonic dementia precox, described in the text. The inequality is striking enough, but each gyrus preserves certain normal features, *e. g.*, the shallower depth of that portion of the gyrus which faces anteriorly. We are here dealing perhaps in large part with a cerebral anomaly.

of the so-called central area was not a property of the postcentral gyrus, but was limited to the precentral gyrus. The general conclusions of Campbell concerning the histology of the gyrus must also be kept in mind, although the work of Holmes and of Brodmann has thrown some doubt upon the details of the gyrus. The question may perhaps remain unsettled, whether we shall count the postcentral gyrus as having two types—one corresponding to the anterior flank, and the other to the posterior—or whether we are to consider that the tissue at the crown of the gyrus represents a novel third type of cortex. Plates IV and V of the case which I shall discuss briefly below, show the range of variation in the cortex types on the sides and at the crown of the postcentral gyri. The anterior face of the postcentral gyrus is normally very thin, and it is clear that both the narrow and the broad postcentral gyri in the case about to be described show in characteristic form the lesser thickness of the cortex on the anterior face than that of the posterior face of this gyrus. It is in this region that Holmes apparently showed Campbell to be in error as to lesions which Campbell thought he had found in the postcentral gyrus of tabes dorsalis. Brodmann unconditionally states that Campbell's findings on the anterior face of the postcentral gyrus are nothing but normal appearances. Brodmann charges Campbell with ascribing pathological changes, cortical atrophy, and cell loss to an area which is in a perfectly normal state. Brodmann somewhat sarcastically says that the situation may be the same in numerous other pieces of work, and he thinks that the so-called pathological changes in the hippocampal region in epilepsy may be perhaps nothing but normal conditions.

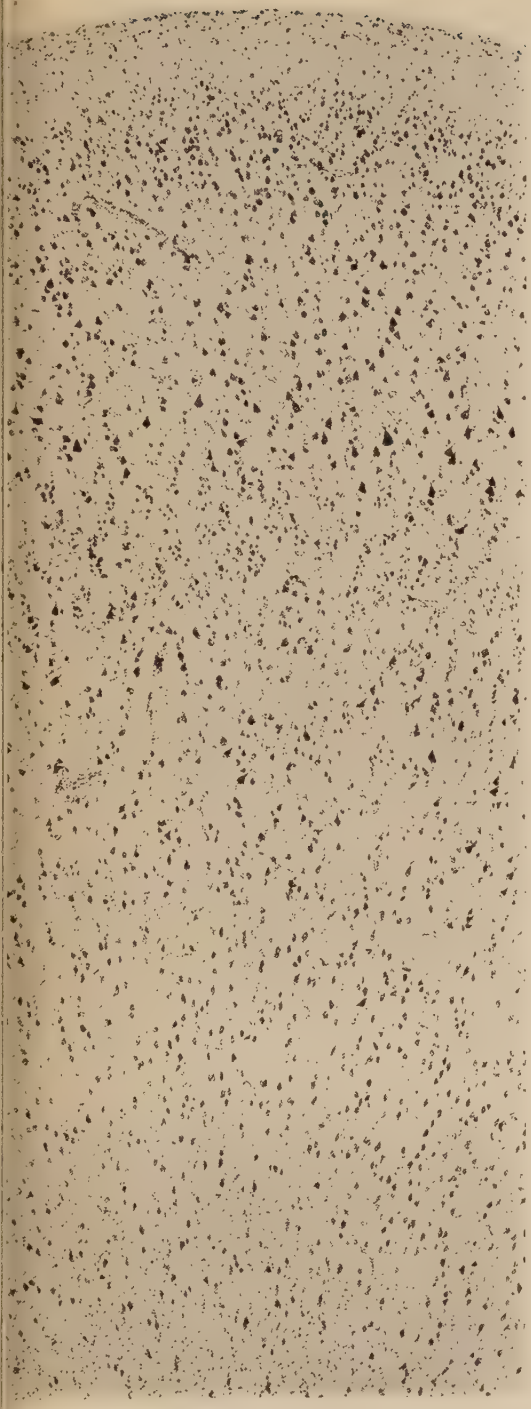
It is clear, however, that in a case like the one to be presented this difficulty does not hold. The reliance of the histopathologist must often be placed on a comparison of coördinate areas on the two sides of the brain. It seems to me that the appearances in Plates IV and V, showing two postcentral gyri in a case of dementia precox, exhibit clearly at least one point, namely: that the gyri differ in some respects at least. Whether the change represents an atrophy and a hypoplasia or a hypogenesia, is a question which cannot be settled without the most elaborate study.

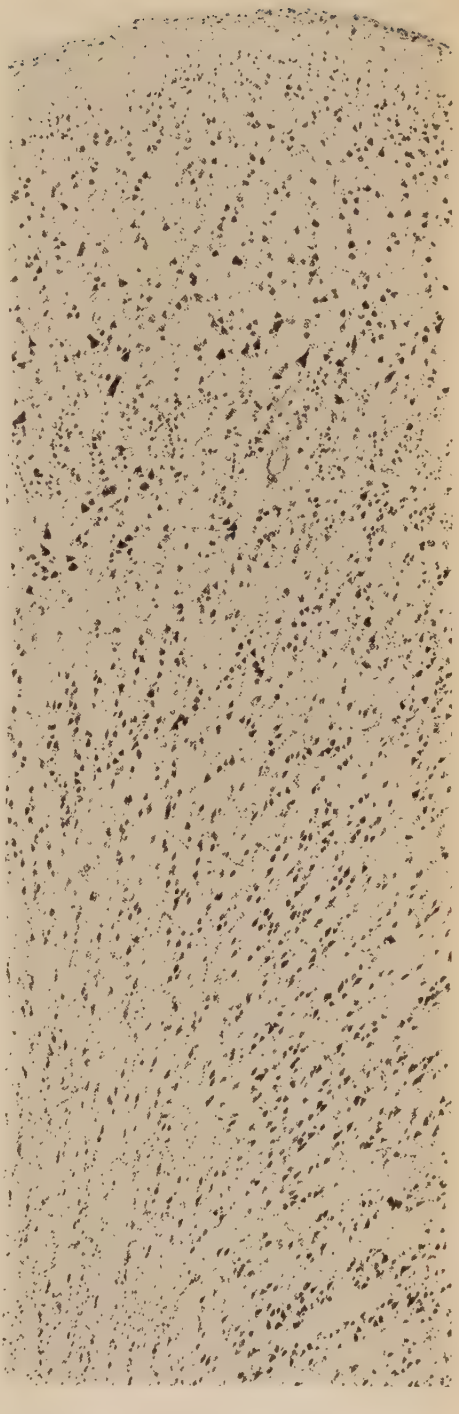
For the moment I desire to make but one point, namely: that we

DESCRIPTION OF PLATES VI TO XI

Plates VI to XI show appearances with higher magnifications from the gyri in catatonic dementia precox shown in low power in Plates IV and V.

Plates VI and VII contrast strips from the crown of the left (larger) and right (smaller) gyri, respectively. *Although it might have been supposed that the smaller gyrus would appear more diseased than the larger,* in point of fact far more satellitosis is discernible in Plate VI (from the "larger" and more grossly normal-looking gyrus). The point is, perhaps, that the right postcentral gyrus had long since passed through and by the phase of satellitosis (or, was it never capable of such reaction?). Of course, the small right gyrus does show relative poverty of *nerve* cells.





have two different conditions with respect to neuroglia proliferation held in the gyri; but before proceeding to speak of this, I wish to sum up the somewhat meagre clinical findings in the case, which has not hitherto been published. The data are as follows:

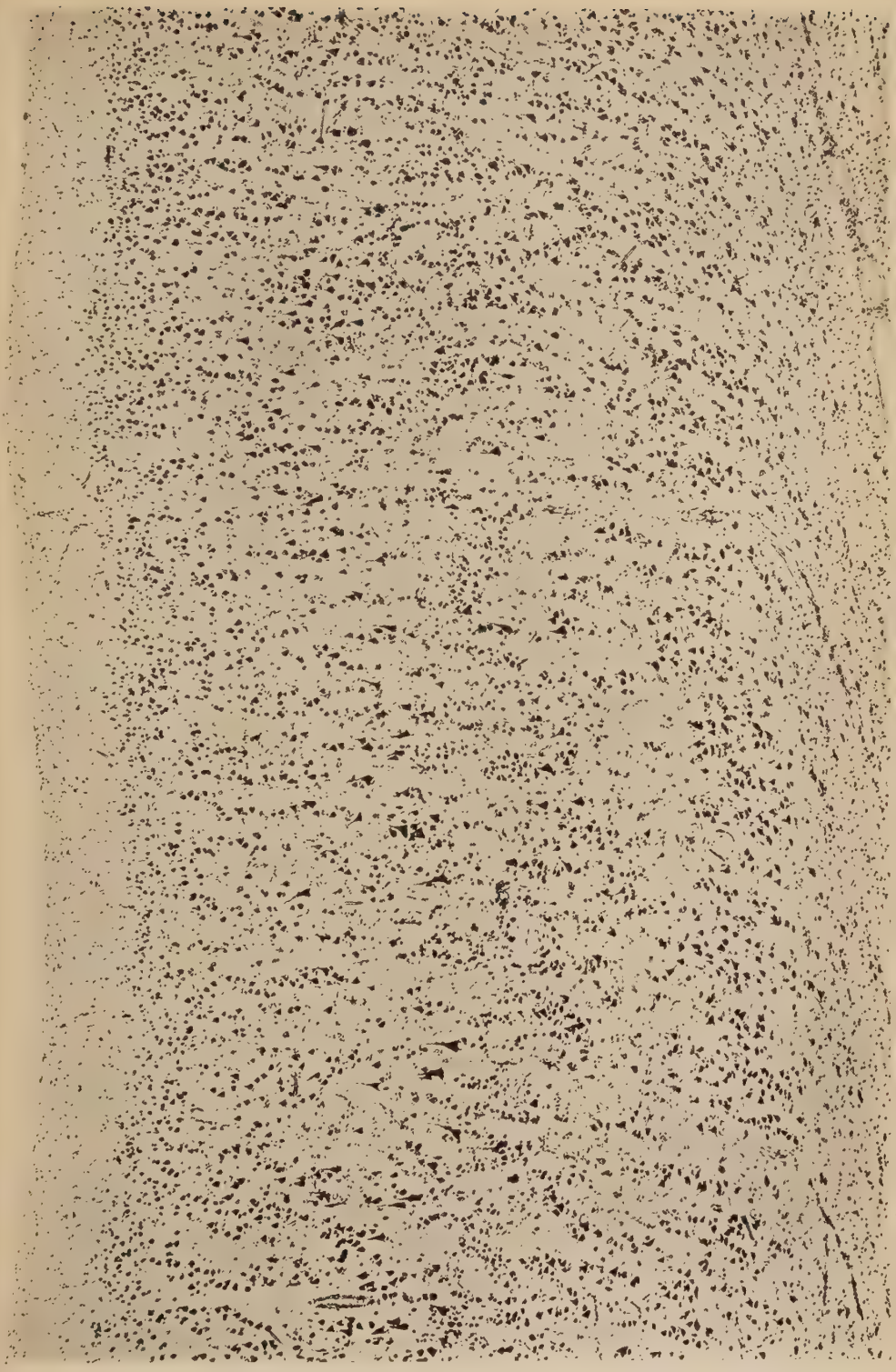
P. F., No. 8300, Danvers[8] Path. Lab., 1151. Married; housewife (sister insane) of Italo-American stock; had an attack of "confusion" in March, 1896, and then rapidly developed a violent acute mania, causing her commitment on the third day, June 22, 1896, at the age of twenty-seven years. The attack apparently began with confusion, mixing baby's milk (patient still lactating, but age of baby not known), followed by anorexia and insomnia, bewilderment, apprehensiveness, declamatory perseveration ("forgive and forget"), spells of hilarity, carelessness in appearance, untidiness. Patient improved in hospital but had spells of confusion and persisted in untidiness. Plunge baths failed to affect the condition. Desiccated thyroid (February, 1897) increased the pulse rate and markedly weakened the patient; but the mental state was improved and the patient became only occasionally untidy. March: stupor and spoon-feeding, untidiness; spells of excitement and glass-breaking. Then relapsed into a quiet apathy with excitement at menstrual periods. Periods of catalepsy (no details available); mutism with occasional laughter at things going on. Variable course, for the most part apathetic, but with spells of elation, singing, laughing, denudativeness, destructiveness, untidiness (June, 1900). Occasionally mute and resistive. In apathy sat in stereotyped position for hours, resisting efforts to change it. Walking with other patients would habitually keep hands over eyes. Periods, so characterized, alternated irregularly for several years. By 1905, the patient had become more antisocial, making violent attacks on patients, climbing on window sills and under tables. In 1907, the patient is described as keeping both hands over eyes for about a third of the time, always in one place in the ward, mute. Sudden transition to excited state, in which denudativeness and rolling about the floor became prominent features. Otitis media, constipation, general cutaneous hyperesthesia, and a peculiar hypertension of muscles described as "stiffening," without twitching or opisthotonos. Death after eight days, March 7, 1907.

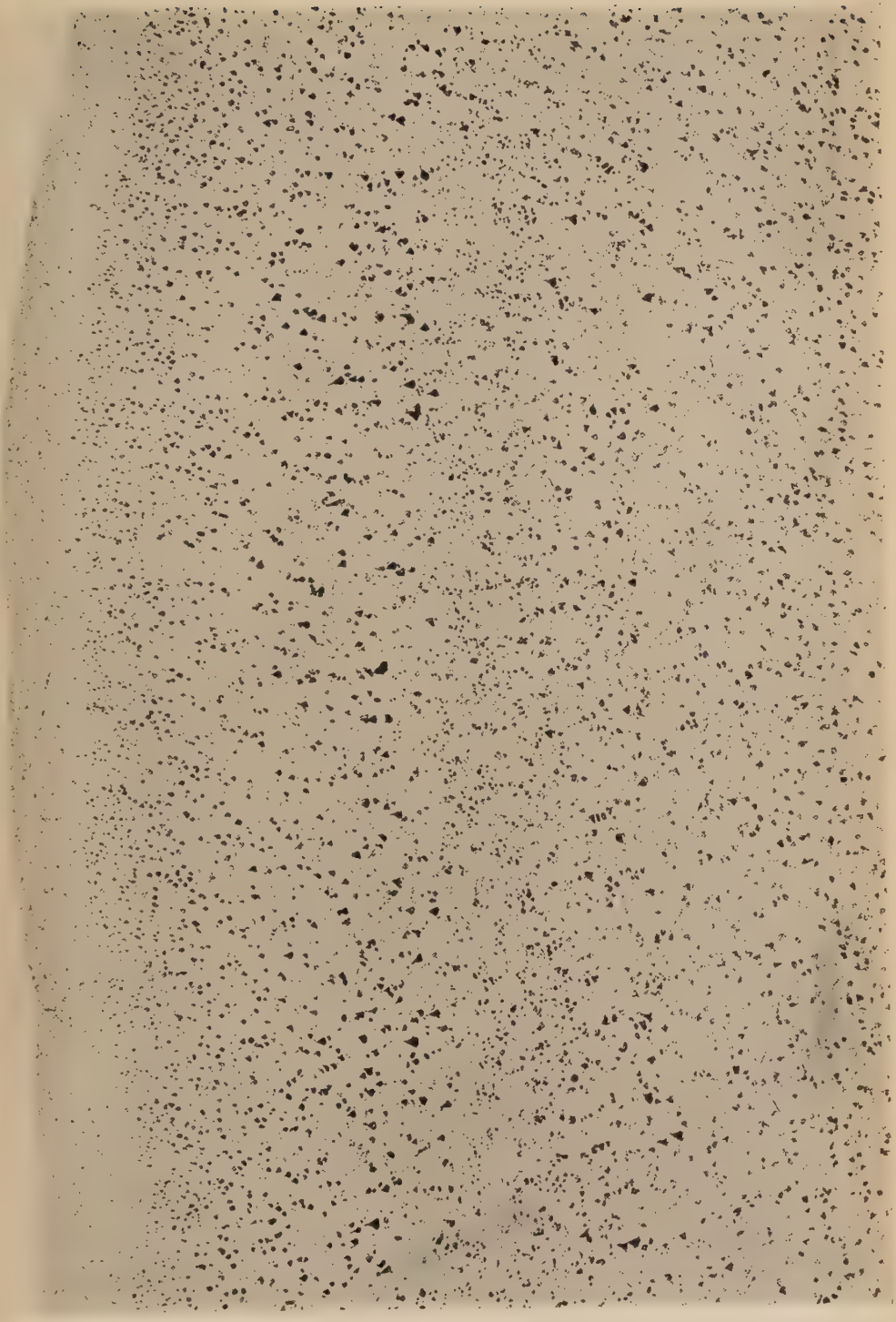
The findings in the head were as follows:

Calvarium not unusual; dura mater non-adherent; pia mater somewhat injected; basal vessels not thickened; brain weight 1045 grams; (by Tigges' formula, the brain weight in a subject 153 cm. long should have been 1224 grams); the cerebellum, pons, and medulla weighed together 150 grams.

DESCRIPTION OF PLATES VIII AND IX

Plates VIII and IX, similarly contrast strips from the posterior faces of the right (or small-looking) and the left (or normal-looking) gyrus. Possibly there is nerve-cell poverty in both gyri. There is far more evidence of satellitosis in the more normal-looking gyrus (compare statement under Plates V and VI).





The anatomical findings in general indicated either an atrophy or a hypoplasia. The general consistence of the brain was firm. (This might and probably does indicate gliosis, but gliosis is no proof that there was not originally a hypoplasia upon which the indurative process has supervened.)

The frontal convolutions were small; *the right postcentral convolution was about half the size of the left*; there were small cysts in the basal ganglia described as "superior to the knee of the internal capsule on both sides." The pia mater over the vermis of the cerebellum is described as "thickened and edematous." The cause of death was broncho-pneumonia with pleuritis, and there was also an acute dysentery.

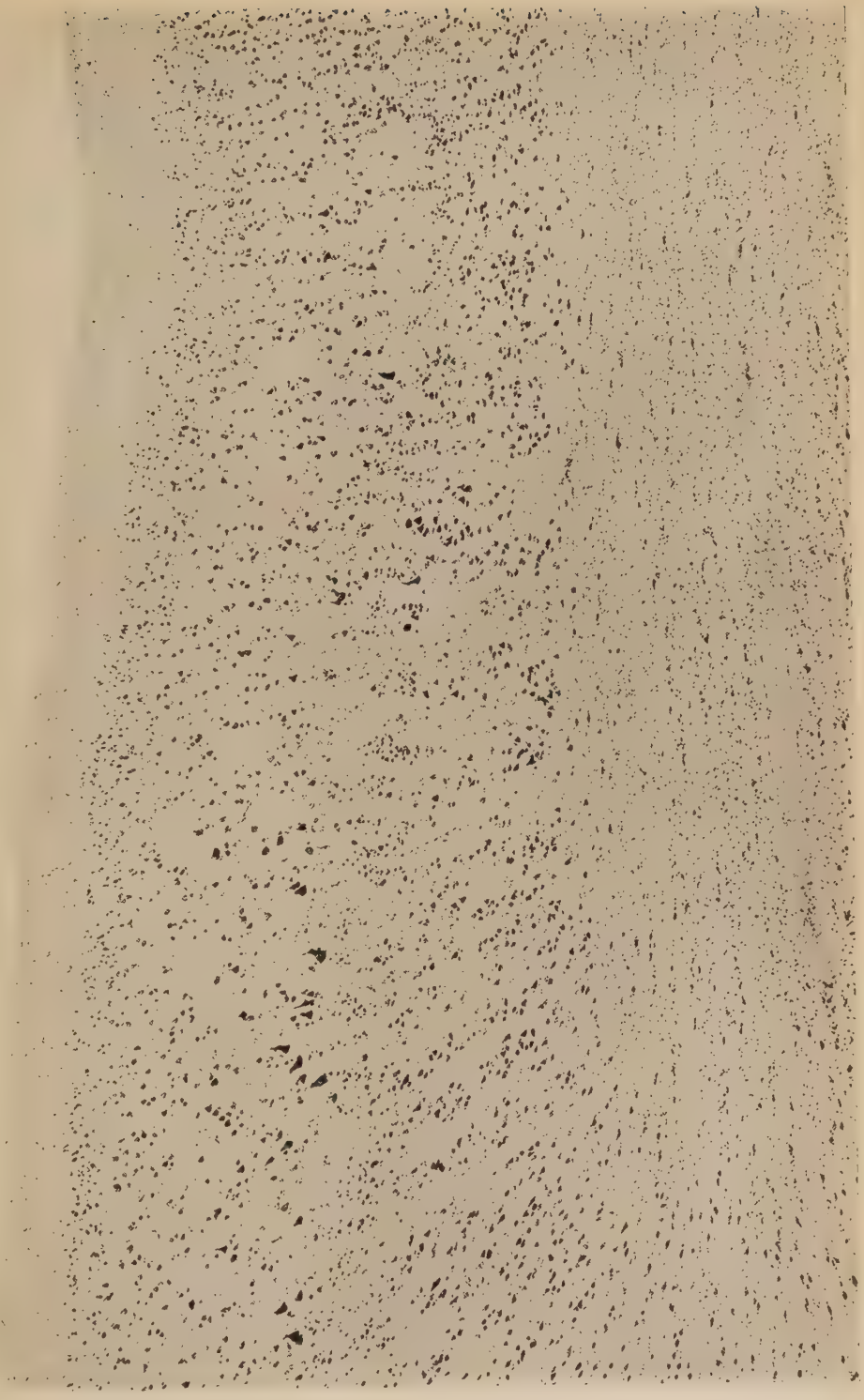
The kidneys showed a chronic diffuse process; there was a slight aortic sclerosis; there were a few milk patches on the pericardium; there was cholelithiasis and chronic splenitis, there was evidence of small old hemorrhages of the pelvic peritoneum and omentum; there was an erosion of the left acetabulum (with anomalous position of the head of the femur).

There is no need to discuss in this place the claims made by the writer as to the correlation of catatonia with post-Rolandic regions and of that exquisite phenomenon of catatonia known as cerea flexibitas with lesions of the postcentral gyrus. The present case was catatonic at times, and there appears to have been a "muscle stiffening" phenomenon, somewhat comparable to cerea flexibilitas. However, whatever the truth may be as to the correlation between the postcentral gyrus regions and muscular hypertension shown clinically, it is at least of importance to consider a fact in the histopathology. This fact is the rather striking fact that the best evidence of satellitosis is found, not in the narrow gyrus, but in the broad gyrus. Accordingly, if one were of a mind to regard the narrowing of the gyrus on the right side as due to an acquired disease process, one must consider that said process has been carried through to a virtual conclusion, and that the satellitosis and neuroglia cell proliferation which may have marked its course has disappeared. Further details are given in description of plates.

Summary and Conclusions.—In the above communication I have endeavored to bring out what I regard as an important line of structural research in mental disease. The general point of view on which I stand may be regarded as somatic although the topic which is most important for psychiatry is undoubtedly the functional psychoses (especially dementia precox and manic depressive psy-

DESCRIPTION OF PLATES X AND XI

Plates X and XI once more contrast strips from the two postcentral gyri (X from the right or anomalously small gyrus and XI from the left grossly normal-looking gyrus. Nerve-cell poverty is probably again in evidence in both gyri, although this condition is notoriously hard to diagnosticate. There is no important amount of satellitosis in either of these cortical strips (unless there is a trace on the left side, viz., in Plate XI). But perhaps none should be expected since the anterior face of the postcentral gyrus is doubtless far more sensory (analogous to calcarine occipital tissue) and the posterior face far more elaborative and, as it were, "psychic" (analogous to common occipital tissue).



chosis). In dementia precox I find four-fifths of the cases showing at autopsy certain appearances which may be regarded as anomalies or lesions in some sense. Possibly they should be regarded as *weak places* in the brain structure in which there may be later every evidence of progressive disease. The percentage of cases of dementia precox showing these lesions is 80 per cent. or higher. The percentage in the brains of non-psychopathic subjects has never been properly established, but in the so-called functional mental disease, manic depressive psychosis, I find similar anomalies or lesions in about 20 per cent. of all cases.

Accordingly, I hold that dementia precox is a disease in which cortical stigmata are much more often found than in certain other forms of mental disease and probably decidedly more often than in the normal citizens of the world.

The direction which research should take as to these findings is important. My point of view here is again a structural one. I present some photographs from two cases which indicate what I think will prove a rich line of research. There are two main lines of consideration.

First. We may study the appearances in those tissues which are regarded as the sensory arrival-platforms of the cerebral-cortex (for example, the calcarine type of occipital cortex) and contrast the findings in the sensory arrival-platforms with findings in the elaborative tissues which are adjacent thereto (for example, the common occipital type of cortex in the occipital region just mentioned). It is currently thought that we can safely call the calcarine type the visuo-sensory type and the common occipital type the visuo-psychic part of the cerebral-cortex. When we are able to get under the same cover-glass materials fixed, prepared and stained in the identical manner and observable in the same thickness, we are undoubtedly able to attach much consequence to the results of microscopic examination.

Secondly. We are able in certain cases to use the bilaterality of structures in the brain to help us in our interpretations. I present photographs in another case which illustrate the line which research may well take. One post-central gyrus in this case was about half the thickness of the other.

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